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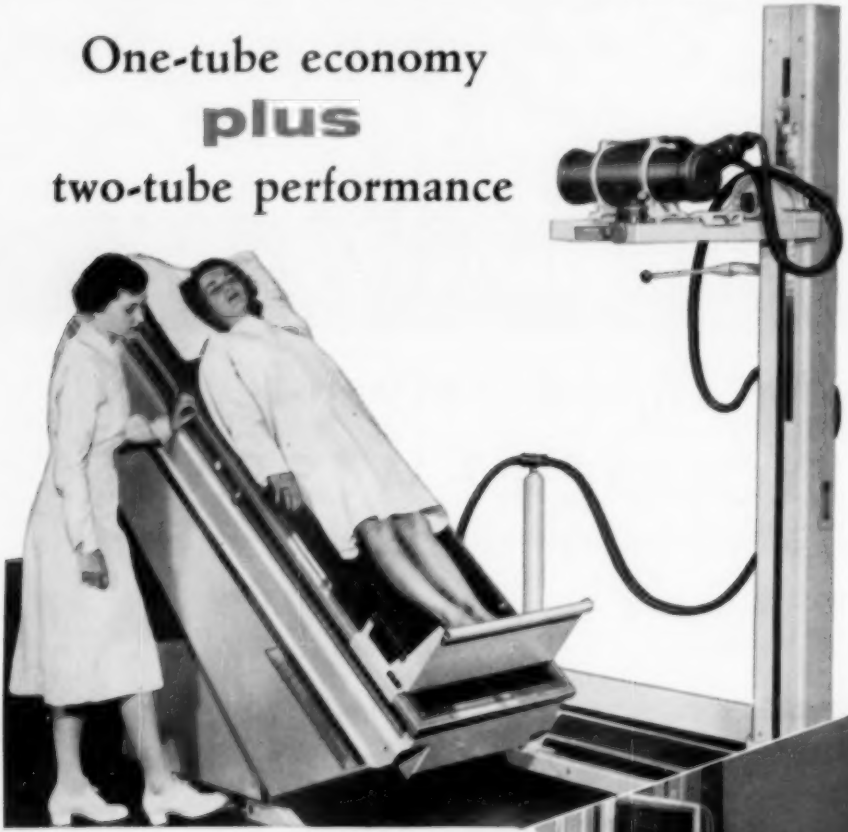

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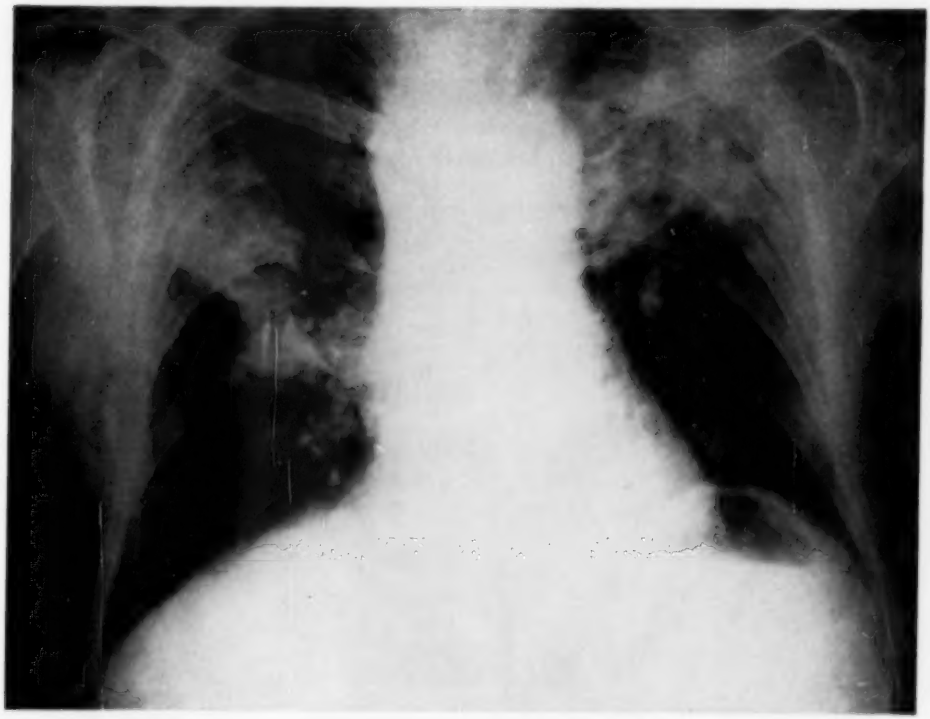

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ERRATUM

In Volume 72, No. 3, 1955, in the Note entitled "An *in Vivo* Method of Culturing Tubercle Bacilli: The Chamber Method" by Shusuke Tsuji and Kaoru Ito, the method of culturing tubercle bacilli referred to as the *benzene* method should have been designated the *benzine* method. The word *benzine* should be substituted for *benzene* in every instance in which the latter word appears.

THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

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PREVENTION OF EXPERIMENTAL TUBERCULOSIS WITH ISONIAZID[1, 2]

SHIRLEY H. FEREBEE AND CARROLL E. PALMER

(Received for publication September 20, 1955)

INTRODUCTION

The demonstrated effectiveness of isoniazid in combating progressive tuberculous disease has quite logically led to the idea that the drug might be effective as a prophylactic: if isoniazid were being taken at the time a tuberculous infection occurred, it might prevent tuberculous disease from developing.

If human beings were protected against tuberculosis while taking isoniazid, appropriate use of the drug might provide entirely new possibilities for the control, perhaps even for the eradication, of human tuberculosis. It is not surprising, therefore, that a number of people have considered these possibilities (1–3). Some (4) have believed that enough is already known to justify the prophylactic use of isoniazid in human beings, especially in countries where tuberculosis is still an acute health problem. Others, although equally aware of the potentialities of the proposition, maintain, nevertheless, that much more should first be learned from carefully controlled studies specifically directed at prophylaxis in both animals and human beings.

In subscribing to the latter point of view, tuberculosis research workers in the Public Health Service have undertaken a series of laboratory studies to determine the preventive effects of isoniazid on experimental tuberculosis in laboratory animals. The present paper reports the first of these studies.

MATERIALS AND METHODS

Study Plan

The experimental studies in animals are being carried out at Chamblee, Georgia, where facilities for large-scale animal experiments are provided by the Communicable Disease Center of the Public Health Service. In general features, the experiments follow the same pattern as the studies on BCG started two years

[1] From the Tuberculosis Program, Division of Special Health Services, Public Health Service.

[2] Presented before the Medical Session, as part of *Section 1B*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 23, 1955.

earlier, which have already been described (5). The present experiment may be briefly outlined as follows:

Approximately 1,200 young guinea pigs were separated into five comparable groups. Three groups of animals received different amounts of isoniazid in their drinking water. For one group the drinking water contained 0.01 mg. per ml.; for another, 0.05 mg. per ml.; and for the third, 0.25 mg. per ml. The drinking water of the animals in the remaining two groups contained no isoniazid. Approximately one month after introduction of the drug, animals in the three groups which received isoniazid, as well as those in a "control" group which did not receive the drug, were given a large intraperitoneal challenge of virulent tubercle bacilli. The fifth group of animals, designated as "normals," also did not receive the drug and were given only a "placebo" instead of the virulent challenge.

Throughout the experiment a variety of observations were systematically made on the animals in all groups: the volume of drinking water consumed per cage was measured, the animals were weighed each week, tuberculin tests were done at approximately monthly intervals, some animals from each group were randomly selected for sacrifice to furnish pathologic information, et cetera.

The most important single observation to be dealt with in this report, however, was the record of the number of days each animal in the experiment survived—material which when combined into data for successive weekly periods provided survival curves for comparing the different groups of guinea pigs.

Ten weeks after the challenge, so many isoniazid-treated animals were still alive that the experiment was modified in two ways. First, isoniazid was discontinued for a randomly selected part of each group which received the drug. The purpose of this change was to determine whether the protection conferred by a ten-week course of isoniazid would continue after the drug was withdrawn.

The second modification, which constituted almost a new experiment, was to introduce a second challenge fourteen weeks after the first. This change in the original experiment made it possible to determine how well guinea pigs would withstand a second virulent infection while they continued to get isoniazid, and how well they would withstand a second infection when they were no longer getting the drug. Neither the controls nor those receiving the 0.01 mg. per ml. concentration of isoniazid were rechallenged because fewer animals in these groups were still living. Animals on the following five schedules were subdivided by random allocation, one part to receive a second virulent challenge, the other a placebo challenge: 0.01 mg. per ml. continuously, 0.05 mg. per ml. for only the first ten weeks, 0.25 mg. per ml. continuously, 0.25 mg. per ml. for ten weeks, and the normals. The portion of the normals challenged at fourteen weeks constituted a "control" group for the second challenge infection.

In figure 1 a time schedule is provided of the administration of isoniazid and the two challenges and the number of animals originally allocated to each of the five main groups is shown as well as the number included in each group or subgroup at each subsequent stage of the experiment.

The animals: Random-bred guinea pigs were selected as suitable animals for the initial experiments because they are readily susceptible to tuberculosis, they resemble human beings in developing tuberculin allergy, they can be obtained in large numbers, and they are relatively easy to manage in the laboratory. Approximately equal numbers of males and females were ordered from a single breeder. At the time of delivery they were four to five

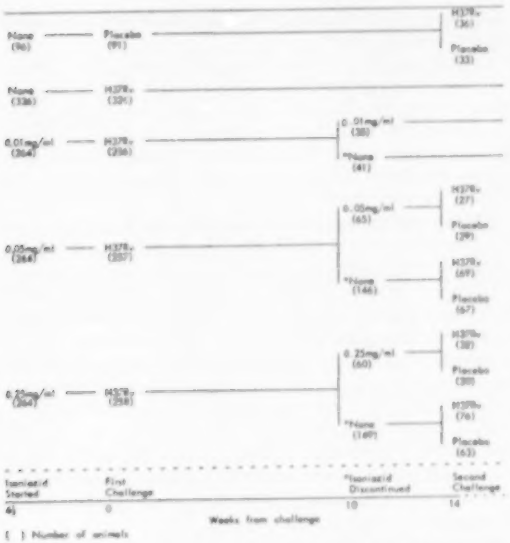

FIG. 1. Distribution of 1,224 guinea pigs among experimental groups and subgroups at each stage of the experiment.

weeks old and most of them weighed from 250 to 350 gm. All were light skinned but differed in hair color. Individual animals were identified by cage number and, within each cage, by an ear punch and a description of hair color.

The protocol of the study called for a total of 1,224 guinea pigs, to be housed in 153 cages (8 of the same sex per cage). By treating each sex as a separate population in the allocation procedures, the ratio of males to females was held equal among the experimental groups. The first step to ensure comparability of the groups was to allocate the animals so that the total weight of the animals in each cage would be approximately equal. The animals were separated into classes according to their body weight and then each weight class was distributed equally among the cages. The next step was to number the cages and allocate them to the five experimental groups in accordance with a table of random numbers. Comparable environmental conditions for the five groups were obtained simply by arranging the 153 cages in the animal quarters in numerical sequence according to cage number.

At the time the cages were allocated to the original five groups, one-third of the cages in each group were randomly identified as a special subgroup from which animals would be drawn for sacrifice. Animals actually sacrificed were then selected at random from the total population in these cages.

Because the isoniazid was to be given in the drinking water, a relatively dry diet was necessary to force the animals to obtain their fluid from drinking water. After considerable experimentation, the diet was restricted to an unlimited supply of a standard guinea pig pellet ration fortified with vitamin C. Its moisture content is estimated to be approximately 9 per cent, and it is claimed to constitute a complete diet for guinea pigs.

Water and drug consumption: In order to determine the dosage of isoniazid, it was necessary to develop a method of supplying drinking water which would permit an accurate estimate of the amount of water consumed per cage. Since it was essential to assume that each pig would drink its portion of water and thus receive its dosage of the drug, the drinking water had to be easily accessible. Furthermore, though accessible, the water had to be pro-

vided in such a way as to avoid spilling and thus ensure that the amount of water used would approximate the amount drunk.

Several months of trial and error with a variety of bottles, tubes, and trays finally led to a device commonly used for watering chickens. It consists of a 2-quart mason jar inverted over a kind of saucer so arranged that the saucer is kept continually filled with water. Several pigs can drink at the same time, but they cannot bathe in it or easily splash it out. In the relatively constant temperature of the air-conditioned quarters in which the animals are housed, approximately 20 ml. of water evaporate each day from a single watering device.

The drinking water of the animals was changed routinely every day, but the amount consumed was measured for only one twenty-four-hour period each week. From the records so obtained it was found that the guinea pigs, on the average, consumed water equivalent to a little more than 10 per cent of their body weight per day. The "normal" animals drank the largest amount, averaging during a period of twenty-six weeks approximately 120 ml. per kg. of body weight per day. Animals which received water that contained the strongest concentration of isoniazid, 0.25 mg. per ml., drank a somewhat smaller amount. As might be expected, cages containing animals which were rapidly dying of tuberculosis showed some reduction in the amount of water consumed: during the first ten weeks after the challenge, animals in the control group drank an average of 99 ml. per kg. per day. Although there was considerable variation from cage to cage in the amount of water consumed, and doubtless a still greater variation in the amount consumed by individual animals, it has been assumed that a satisfactory estimate of the dosage of isoniazid can be obtained from the measurements of drinking water consumed.

In table 1 information is furnished which translates water consumption at various stages of the experiment into isoniazid dosage. The 0.01 mg. per ml. concentration of isoniazid apparently provided slightly more than 1 mg. of the drug per kg. of body weight per day, the 0.05 mg. concentration between 5 and 6 mg. per kg., and the 0.25 mg. concentration slightly more than 25 mg. per kg.

Challenge: Animals scheduled to receive a virulent tuberculous infection were given an intraperitoneal injection of 0.5 ml. of a liquid Tween®-albumin suspension of H37Rv, originally obtained from the Trudeau Laboratory, Saranac Lake, New York. As determined by plate counts, the first challenge contained approximately 5×10^6 viable bacterial units per

TABLE 1

DOSAGE OF ISONIAZID AS COMPUTED FROM DAILY WATER CONSUMPTION, CONCENTRATION OF ISONIAZID, AND BODY WEIGHT

Weeks After Challenge	Average Ml. of Water Consumed per Kg. of Body Weight			Mg. Isoniazid per Kg. of Body Weight		
	0.01 mg/ml	0.05 mg/ml	0.25 mg/ml	0.01 mg/ml	0.05 mg/ml	0.25 mg/ml
0 to 10½ weeks	109	112	103	1.1	5.6	25.8
10½ to 14 weeks						
Still receiving isoniazid	129	116	101	1.3	5.8	25.3
Not receiving isoniazid	101	101	101	—	—	—
14 to 26 weeks						
Still receiving isoniazid						
Rechallenged	—	108	101	—	5.4	25.3
Not rechallenged	n.s.*	111	110	—	5.6	27.5
Not receiving isoniazid						
Rechallenged	—	92	97	—	—	—
Not rechallenged	n.s.*	117	115	—	—	—

* Too few living pigs to give reliable average.

ml., the second challenge 4×10^6 units per ml. Animals which did not receive a virulent infection at the time of either the first or second challenge received a "placebo" injection of 0.5 ml. of the Tween®-albumin culture medium. The placebo challenge was used in order to equalize the possible effects which might result simply from an intraperitoneal injection and the attendant handling of the animals.

RESULTS

The length of life after a challenge with virulent tubercle bacilli is perhaps the simplest single measure of the complex set of factors which together constitute an animal's resistance against a tuberculous infection and has been chosen here as the primary basis for comparing animals on the different regimens. Deaths from causes other than tuberculosis may be expected to occur with equal frequency in all experimental groups, with the result that, in a controlled experiment with strictly randomized groups of sufficient size, the differences in survival can be attributed to the effect of isoniazid. The basic data for computing survival curves are given in table 2: the number of animals which started in each group or subgroup in the various parts of the experiment and the numbers which died, were sacrificed, or were withdrawn for other purposes, each week.

The survival curves following the first challenge are shown in figure 2. A separate curve for each of the original five groups of animals shows the percentage of the total number of guinea pigs which were still alive at successive weeks after the challenge. The survival experience and other related material may best be considered in several separate segments of time, corresponding to the changing conditions of the experiment.

First Ten Weeks After Challenge

During the first ten weeks of the experiment, three groups were receiving isoniazid in dosages of approximately 1, 5, and 25 mg. per kg., respectively. These groups and the infected control animals had received a virulent challenge, whereas the normal animals had received no drug and only a placebo challenge. The control animals died rapidly and by the tenth week only 7 per cent were still alive. The guinea pigs which received 1 mg. of isoniazid per kg. evidently derived some protection from the drug, and at ten weeks 36 per cent were still alive. Animals which received either the 5 or 25 mg. dose of the drug experienced no greater death rates than the normal untreated, uninfected animals. Ten weeks after challenge, 88 per cent of the normal animals, 86 per cent of the animals in the 25 mg. group, and 87 per cent of the animals in the 5 mg. group were living.

The weekly weights of the guinea pigs provide another simple, objective, and quantitative measure of difference among animals in the several experimental groups, and certain parts of the weight data relating to the first ten weeks after challenge are presented in figures 3 and 4.

The average body weights of the guinea pigs in each group at weekly intervals are shown in figure 3. In section *A*, the averages are based on the weights of all animals which were alive at the time of the weekly weighings. All of the five groups showed very nearly the same average weight, approximately 500 gm., at the time of challenge. From the first through the fourth weeks, the untreated pigs

TABLE 2.

NUMBER OF GUINEA PIGS DYING AND SACRIFICED IN VARIOUS EXPERIMENTAL GROUPS BY WEEK

Weeks	Normals		Controls		1 Mg. of Isoniazid		5 Mg. of Isoniazid		25 Mg. of Isoniazid	
Number living at start of study	96		336		264		264		264	
Number dying before challenge	5		10		8		7		6	
Number living at first challenge	91—Placebo		326—H37Rv		256—H37Rv		257—H37Rv		258—H37Rv	
	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed
0 < 1	1	1	9	2	2	1	6	1	9	1
1 < 2	2	—	8	1	9	1	5	—	5	—
2 < 3	2	—	31	1	16	1	1	—	2	1
3 < 4	1	1	32	1	8	1	3	—	—	1
4 < 5	1	—	61	1	21	1	1	1	3	1
5 < 6	1	—	63	1	27	2	—	1	4	2
6 < 7	1	1	36	3	28	2	2	3	4	2
7 < 8	2	1	31	3	19	3	7	2	2	2
8 < 9	—	1	10	3	15	3	2	2	2	2
9 < 10	—	1	10	1	12	2	5	1	4	1
10 < 10½	—	—	5		6	—	3	—	1	—
Number living in subgroups					35—1 mg.	41—none	65—5 mg.	146—none	60—25 mg.	149—none
					Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed
10½ < 11	—	—	2		1	1	3	1	1	1	—	1	1	1	—	—
11 < 12	—	1	1		1	3	1	3	—	2	4	2	1	2	—	2
12 < 13	1	1	4		—	3	1	3	1	2	—	2	—	2	1	2
13 < 14	1	1	2		2	2	3	2	1	1	—	1	—	1	3	2

TABLE 2—CONTINUED

Number living at second challenge	33—placebo		36—H37Rv								29—placebo		27—H37Rv		67—placebo		69—H37Rv		29—placebo		32—H37Rv		63—placebo		76—H37Rv	
	Dead	Sacrificed	Dead	Sacrificed							Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed	Dead	Sacrificed
14 < 15	—	1*	2	3	—		2		2		1	7*	1	7*	2	13*	1	13*	—	7*	3	6*	2	11*	3	15*
15 < 16	—	1	—	2	2		—		4		1	1	2	2	—	1	—	2	—	1	—	2	—	1	2	2
16 < 17	1	1	3	2	—		2		—		—	1	—	3	—	1	1	2	—	2	—	3	—	1	2	2
17 < 18	—	1	6	1	—		—		2		—		—	1	1	1	1	1	—		—	1	1		4	1
18 < 19	1		5		—		2		3		—		—		2		1		—		—		—		2	
19 < 20	1		4		1		—		3		1		—		1		3		—		—		—		4	
20 < 21	—		1		—		—		—		—		—		1		4		—		1		1		2	
21 < 22	—		1		1		—		1		—		—		—		4		—		—		—		5	
22 < 23	—		1				—		—		—		—		—		2		—		1		—		6	
23 < 24	—		—				—		—		1		—		—		7		—		—		—		3	
24 < 25	1		3				1		—		—		—		—		4		—		—		—		2	
25 < 26	1		—				1		—		—		—		—		3		—		1		—		3	
26 < 27	—	24†	—				1		—		—	16†	—	11†	—	30†	3		—	10†	—	14†	—	29†	3	
27 < 28			—				—		1						1		1						—		1	
28 < 29			1				—		—						—		1						—		2	
29 < 30			—				1		—						—		—						—		1	
30 < 31			—				—		—						—		2						—		3	
31 < 32			—				1		1						—		—						—		2	
32 < 33			—				—		—						—		3						—		2	
33 < 34			—				—		—						—		1						—		2	
34 < 35			1				—		—						1		3						1		—	
35 < 36							1		—						1		2						1		1	
36 < 37							—		1						—		2						6		—	
37 < 38							1		—						—		—						1		—	
Number living at thirty-eighth week							9		6						11		2						8		1	
Column number...	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)	(25)	(26)

* Included, and shown as sacrificed in the fourteenth week, are 68 animals which died within 48 hours of the time of the second challenge. These deaths, it has been assumed, were due to hypersensitivity to a second injection of Tween*-albumin medium which had been created by the first challenge injection containing H37Rv in Tween*-albumin medium, with one exception, i.e., they did not occur among animals which previously had had the placebo injection *containing only the Tween*-albumin medium*; they occurred only among animals that previously had had an injection *containing both H37Rv and Tween*-albumin medium*, and in these groups they occurred whether the second challenge contained H37Rv and Tween*-albumin medium or only Tween*-albumin medium. The distribution of the 68 deaths is as follows: 1 in column 2; 6 in column 12; 5 in column 14; 13 in column 16; 10 in column 18; 7 in column 20; 4 in column 22; 10 in column 24; and 12 in column 26.

† Withdrawn from study for pilot trials during the twenty-sixth week.

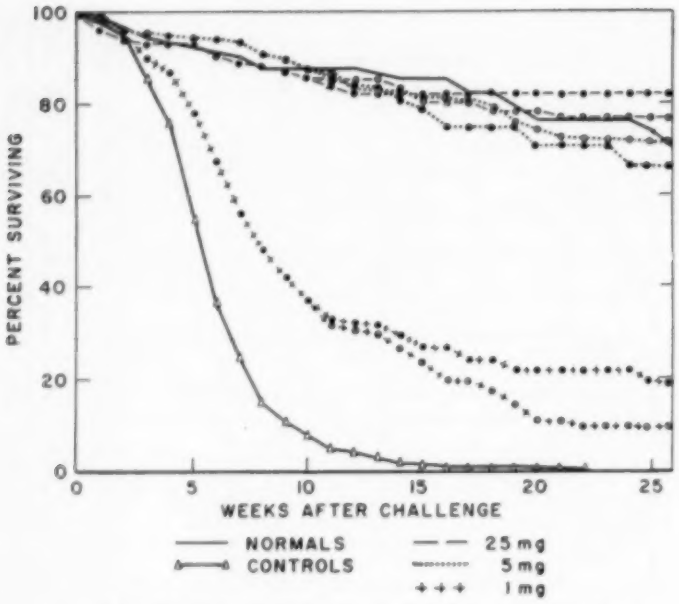

FIG. 2. Percentage of guinea pigs surviving at each of twenty-six weeks after challenge infection with virulent tubercle bacilli.

in the control group lost weight and then remained practically stationary, on the average approximately 60 gm. under their challenge weight. Animals which received 1 mg. of isoniazid lost weight until the third week after challenge and then gained slowly but steadily to reach an average of a little more than 600 gm. in the tenth week. Animals which received either 5 or 25 mg., however, did not lose after challenge. They gained steadily at the same rate as the normal animals to an average of approximately 675 gm. in the tenth week.

In section *B* of figure 3, the weekly averages are based on the weights of only the guinea pigs which were living ten weeks after challenge, excluding the weights of all pigs which died during this period. This section of figure 3 gives the added information that the differences between the weights of animals in the different groups are not simply a reflection of the greater mortality in the control and 1 mg. groups. Not only did fewer of the control animals and the pigs in the 1 mg. group survive but, as this figure indicates, those which were still alive at ten weeks were definitely less healthy, as judged by body weight, than the normal animals and those in the 5 mg. and 25 mg. groups. Guinea pigs which received the 5 or 25 mg. doses not only survived in the same proportion as the normals, but, in addition, the survivors increased in weight as much as the normal uninfected animals.

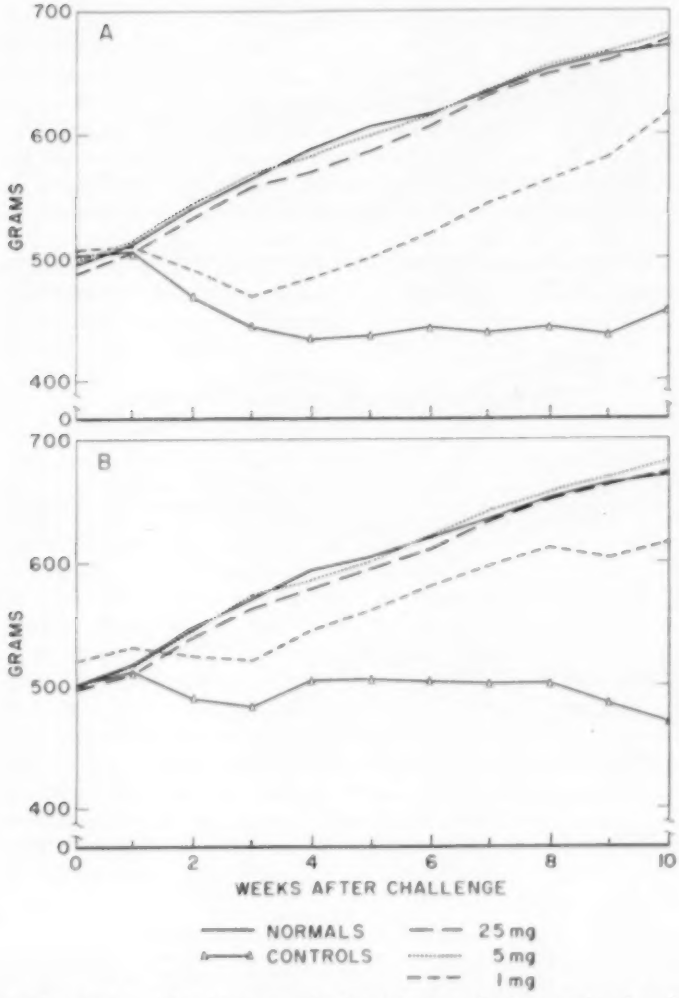

FIG. 3. Mean body weight of 5 groups of guinea pigs at each of ten weeks after challenge infection with virulent tubercle bacilli; *A*—mean for each week based on all guinea pigs alive that week; *B*—mean for each week based only on guinea pigs living at least ten weeks.

Loss of weight was closely related to length of survival of the guinea pigs, and marked decreases in weight usually occurred in the two weeks preceding death. This relation is illustrated in figure 4, which is based on observations from the two-thirds of the experiment from which animals were not sacrificed. For this particular analysis, the guinea pigs have been subdivided by the number of weeks they survived. The average weekly weights for the first ten weeks are shown in separate curves for those which died each week and those still living in

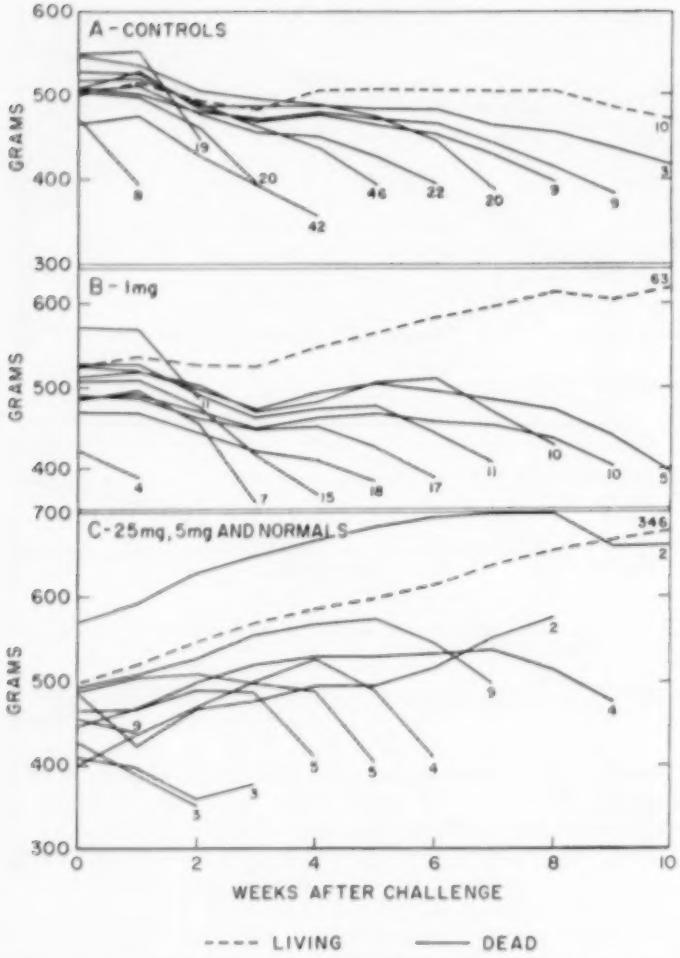

FIG. 4. Mean body weight of guinea pigs, subdivided by length of survival, at each of ten weeks after challenge infection with virulent tubercle bacilli: *A*—controls, *B*—1 mg. per kg., *C*—25 mg. per kg., 5 mg. per kg., and normals.

the tenth week. Data for the control animals are shown in section *A* of the figure; for the 1 mg. group, in section *B*; and for the 5 mg. and 25 mg. groups and the normal animals, the data are combined in section *C*.

Comparison of sections *A* and *B* shows that the weight pattern of the pigs which died during the first ten weeks was very similar for the control animals and for the pigs which received 1 mg. of isoniazid, although a greater number of deaths occurred among the control animals. In both groups, the animals tended to lose weight during the first three weeks after challenge. Those which survived

this initial period, however, usually gained slightly, only to lose weight sharply again two weeks before they died.

Deaths were so infrequent among the normal animals and the animals which received 5 or 25 mg. of isoniazid that the three groups were combined to obtain enough material to analyze the weight changes before death. In general, changes in weight before death were rather variable in these groups, and there was little evidence of a loss in weight during the first three weeks after challenge similar to the loss observed in the control and the 1 mg. groups. Another point may also be noted: the average weight at challenge of guinea pigs which died during the first ten weeks was almost always below the average weight of pigs which lived beyond the tenth week. There seems to be, therefore, a relation between the initial weight and the length of survival in guinea pigs apparently free of tuberculosis.

Eleven to Twenty-Six Weeks After Challenge

After ten weeks isoniazid was removed from the drinking water of a part of the three groups of guinea pigs which received the drug in order to investigate the effect on the tuberculous infection. A part of each group continued to receive isoniazid, however, to provide a basis for comparison. The resulting survival curves for the eleventh through the twenty-sixth weeks are included in figure 2.

When isoniazid was discontinued in the group which received the 1 mg. dose, the guinea pigs died a little more rapidly than when administration of the drug was continued. By the twenty-sixth week, only 10 per cent of the animals which received no drug and 19 per cent of those which continued to receive the drug were still alive. The survival curves for the 5 mg. and 25 mg. groups of animals did not differ consistently from the survival of the normal animal group, irrespective of whether isoniazid had been administered after the first ten weeks. Surviving in the twenty-sixth week were 71 per cent of the normal animals, 83 per cent of the pigs which had received 25 mg. continuously, and 77 per cent of those treated on the 25 mg. regimen for only ten weeks, 66 per cent of those which received the 5 mg. dosage continuously, and 72 per cent of those treated on the 5 mg. regimen for ten weeks.

Second Challenge

By the fourteenth week, enough pigs were still alive, except in the 1 mg. and control groups, to study the effect of a second virulent challenge under two circumstances, first when both challenges were accompanied by the daily administration of isoniazid and, second, when isoniazid was discontinued before the second challenge.

In figure 5, the survival of the animals in the subgroups which received a virulent challenge at fourteen weeks is shown. The mortality among the new control group was very much like that experienced by the controls which received the original challenge: by the twenty-fourth week of the experiment, ten weeks after their challenge, only 18 per cent were alive; and by the thirty-fifth week, all animals were dead.

The open circles are used in figure 5 for rechallenged animals which had re-

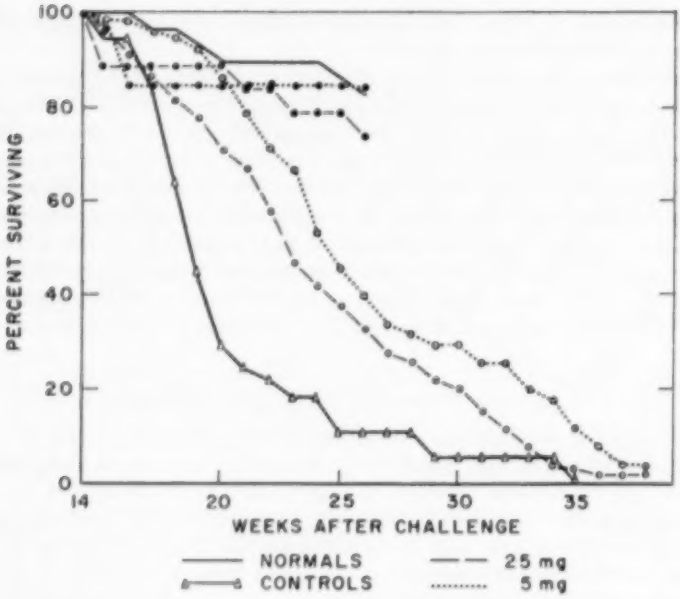

FIG. 5. Percentage of guinea pigs surviving each week after second challenge infection with virulent tubercle bacilli fourteen weeks after first challenge.

ceived either the 5 or the 25 mg. isoniazid regimen for only the first ten weeks. These animals survived the second challenge better than the control animals, even though the animals in this group were no longer receiving isoniazid. The guinea pigs which had received the 5 mg. regimen daily during the first infection were apparently a little better protected against the second challenge than those which had received the 25 mg. dosage. By the thirty-fourth week, twenty weeks after the second challenge, 18 per cent of the 5 mg. group and only 4 per cent of the 25 mg. group of animals were still living.

The lines with solid circles in figure 5 show the survival experience of the pigs which received the 5 or 25 mg. isoniazid dosage continuously during two challenge infections; the solid line is used to indicate survival of the normal animals. All three of these groups were relatively small at the time of the second challenge and, as a result, the survival curves are somewhat irregular. Moreover, the curves are shown for only twelve weeks after the second challenge because at that time the animals still alive in these groups were withdrawn and used for other experiments. The differences in the survival experience of the three groups were not statistically significant for the twelve-week period. Other evidence not presented here supports the view that the daily administration of either 5 or 25 mg.

of isoniazid protected the guinea pigs against not only one, but two, large intraperitoneal infections with virulent tubercle bacilli.

Body Weight

The results of the weekly weighing of the animals included in most of the different subgroups are shown in figure 6 for a ten-week period after the second

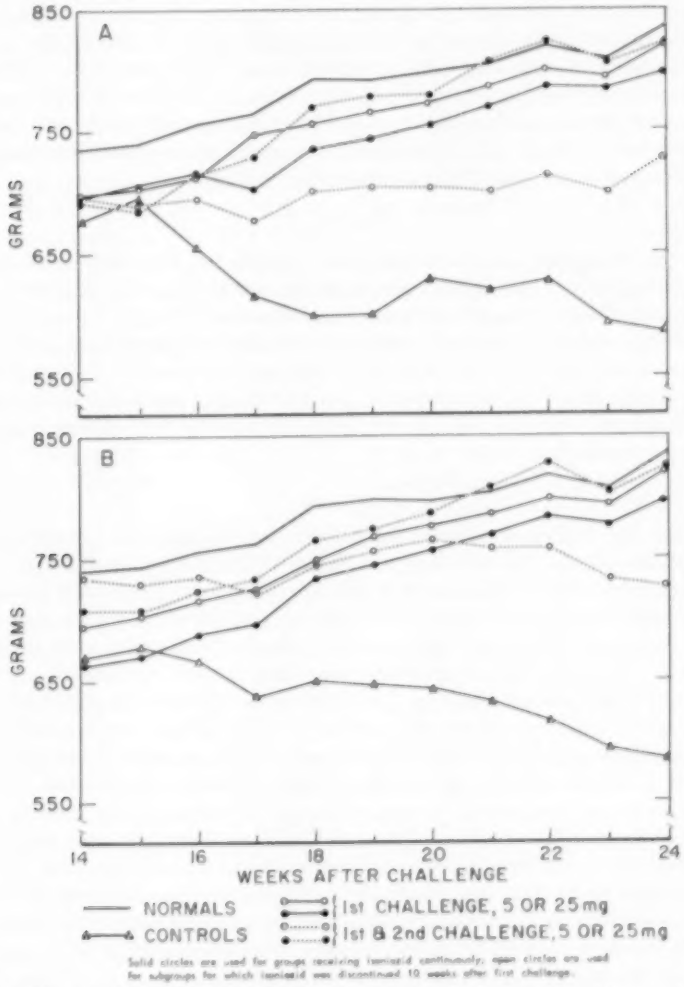

FIG. 6. Mean body weight of selected groups of guinea pigs at each of ten weeks after second challenge infection with virulent tubercle bacilli: *A*—mean for each week based on all guinea pigs alive that week; *B*—mean for each week based only on guinea pigs living at least ten weeks.

challenge (from the fourteenth to the twenty-fourth week after the first challenge). The data are presented in the same way as in figure 3 except that the 5 and 25 mg. subgroups have been combined because no important differences in the weight data were observed among animals given the two different doses of the drug. In section *A*, as in figure 3, the weekly averages are based on all animals alive at the time of the weekly weighings; in section *B*, the averages are only for the animals which were living ten weeks after the second challenge. In general, the results confirm and extend the analysis of the weights of the animals after the first challenge although the curves are more irregular because they are based on rather small numbers of animals. The most significant additional observation is that animals which had had the first virulent challenge, and had received either 5 or 25 mg. of isoniazid for only ten weeks, continued to gain in weight as well as the untreated, uninfected normal animals.

Toxicity

Several observations provide indirect evidence of the absence of serious isoniazid toxicity in the dosages used and for the periods of time given in this experiment. The fact that there were no more deaths in the 5 or 25 mg. isoniazid groups than among the normal animals indicates that isoniazid toxicity was not a cause of death. The absence of toxicity was also suggested by the material on body weight: there was no indication that guinea pigs which received even the highest dose of isoniazid, 25 mg. per kg., differed from the normal animals in terms of progressive increase in weight.

DISCUSSION

Within the period of observation afforded by the present experiment, the prophylactic effects of isoniazid appear definitive in three respects. First, a small amount of isoniazid administered in the drinking water prevented a large intraperitoneal inoculum of virulent tubercle bacilli from either killing guinea pigs or interfering with their growth in weight. Second, the effects of giving the drug appear to be more than a temporary "holding action" because deaths from tuberculosis did not occur during the sixteen-week observation period after the drug was discontinued and the animals continued to gain as much weight as the normal guinea pigs. Third, the isoniazid-protected challenge with tubercle bacilli resulted in the animals' developing a considerable degree of resistance to a later unprotected challenge with a comparable inoculum of bacilli. It may be noted that the degree of acquired resistance observed appears to be comparable with that produced by vaccinating guinea pigs with BCG (6, 7). These findings are in general agreement with the prophylactic effects of isoniazid noted by several other workers in the course of studies on the therapeutic properties of the drug (8–16). The results are certainly encouraging enough to justify further large-scale trials on the prevention of tuberculosis with isoniazid.

Among the most obvious problems needing further study are questions of the dosage of the drug and the frequency and duration of its administration. The results of the present study indicate the outside limits within which an "opti-

mum" daily dose may lie and also suggest several criteria for judging an optimum dose. First, tuberculous disease should not develop after a virulent challenge while the animal is receiving isoniazid; second, tuberculosis should not become manifest after the drug has been discontinued; and third, maximum resistance to a later untreated infection should be created during the first isoniazid-protected infection.

The 5 mg. per kg. daily dose of isoniazid was apparently sufficient to protect the guinea pigs against an initial infection during the period when the drug was being given and, also, after its administration had been discontinued. The 1 mg. dose provided only partial protection while it was being administered and even less after it had been discontinued. Hence, the 1 mg. regimen can be discarded as unacceptable for chemoprophylaxis in guinea pigs on the basis of its effect on the first challenge infection. The results of a second challenge, given after isoniazid had been withdrawn, suggest that the 5 mg. isoniazid regimen is preferable to the 25 mg. regimen. Although a dose of 5 mg. of isoniazid per kg. was high enough after the initial infection, it may have been higher than was needed. Moreover, as the 5 mg. dosage regimen was associated with the appearance of a greater degree of host resistance in the guinea pigs against a later untreated infection than the 25 mg. regimen, it is possible that an isoniazid regimen lower than 5 mg. per kg. would be associated with an even higher degree of acquired resistance of the guinea pigs.

Experience with daily dosages of the 1, 5, and 25 mg. isoniazid regimens under the conditions of the present experiment thus seem to indicate that the optimum prophylactic dose should lie somewhere between 1 and 5 mg. per kg. per day. Experiments in this dosage range are now underway to try to find a dose as effective during the initial infection as the 5 mg. dosage but one which will allow maximum resistance to develop against a subsequent infection. Additional experiments, which may be especially pertinent for planning and interpreting trials on the prevention of human tuberculosis, have also been started to determine the effectiveness of giving the drug intermittently and for short periods of time.

In interpreting the results of the present study, it should be noted that isoniazid was placed in the animals' drinking water for about one month before the first challenge was given. This was not done because a long pretreatment period was considered necessary but in order to gain experience in the problems of administering the drug, especially to learn whether guinea pigs would continue to drink water containing moderately high concentrations of isoniazid. Later experiments have indicated that results similar to those reported here are obtained when the drug is started only two days before the challenge. The reports of several other workers cite equally favorable results even though isoniazid was started after the challenge. Altogether, these provide indirect evidence that pretreatment with isoniazid was not a necessary condition for the protection provided against the virulent infection.

Results of tuberculin testing are not included in the present paper but will be reported later, together with material from other experiments. The pathologic and/or bacteriologic findings are not reported because only a relatively few

animals were sacrificed. These animals were used primarily to study methods and techniques (particularly organ counts of viable tubercle bacilli) which could be applied in later experiments.

SUMMARY

Results are reported from the first of a series of studies on the prophylactic use of isoniazid in experimental tuberculosis in guinea pigs. Altogether, 1,224 young guinea pigs were randomly separated into a number of groups and subgroups; some groups were given the drug and challenged with a large intraperitoneal inoculum of virulent tubercle bacilli, other groups were held as various types of "controls." Isoniazid was administered in the drinking water in three different concentrations so that some groups of animals received on the average approximately 1 mg., others 5 mg., and others 25 mg. of isoniazid per kg. of body weight per day.

Two main conclusions are drawn from the study: *(1)* A daily dose of as much as 5 mg. per kg. of isoniazid, if started before the challenge infection and continued for only ten weeks after the challenge, is apparently sufficient to prevent mortality from tuberculosis for at least the twenty-six weeks observed here, and to allow the guinea pigs to grow in weight at the same rate as normal untreated, uninfected pigs. *(2)* It also appears that, after an isoniazid-treated tuberculous infection, guinea pigs respond to a later, untreated tuberculous infection very much as they do after vaccination with BCG.

SUMARIO

Prevención de la Tuberculosis Experimental con Isoniacida

Preséntanse los resultados del primero de una serie de estudios relativos al empleo profiláctico de la isoniacida en la tuberculosis experimental de los cobayos. En conjunto, se separaron al azar 1,224 cobayos jóvenes en varios grupos y subgrupos; algunos grupos recibieron la droga y fueron tanteados con un gran inóculo intraperitoneal de bacilos tuberculosos virulentos; otros grupos fueron mantenidos como varias clases de "testigos." La isoniacida fué administrada en el agua de bebida a tres diferentes concentraciones, de modo que algunos grupos de animales recibieron por término medio aproximadamente 1 mg.; otros, 5 mgs.; y otros, 25 mgs. de isoniacida por kg. de peso vivo al día.

Del estudio se sacan dos conclusiones principales: *(1)* una dosis diaria hasta de 5 mgs. de isoniacida por kg. de peso, si se inicia antes de la infección provocadora y continuada solamenta diez semanas después de la provocación, basta aparentemente para impedir la mortalidadad por tuberculosis, a lo menos durante las veinte y seis semanas de observación en este caso, y para permitir que los cobayos aumenten de peso con la misma velocidad que los cobayos indemnes, no tratados, normales. (2) También parece que, después de una infección tuberculosa tratada con isoniacida, los cobayos responden a una infección tuberculosa no tratada subsiguientemente en forma muy semejante a la que lo hacen después de la vacunación con BCG.

RESUME

Prévention de la tuberculose expérimentale par l'isoniazide

Les auteurs rapportent les résultats de la première étude, parmi une série de recherches sur l'emploi de l'isoniazide à titre prophylactique dans la tuberculose expérimentale du

cobaye. En tout, 1.224 jeunes cobayes ont été répartis au hasard dans un certain nombre de groupes et de sous-groupes, certains groupes recevaient l'antibiotique et ils étaient en suite soumis a l'epreuve de l'inoculation intrapéritonéale d'une quantité importante de bacilles tuberculeux; d'autres groupes étaient réservés au titre de différents types "témoins." L'isoniazide était administrée à trois concentrations différentes, dans l'eau de boisson, de telle sorte que certains groupes d'animaux recevaient en moyenne approximativement 1 mg; d'autres, 5 mg; et d'autres 25 mg d'isoniazide par kg de poids du corps par jour.

Deux conclusions principales sont tirées de cette étude: (*1*) une dose quotidienne atteignant jusqu'à 5 mg/kg d'isoniazide, lorsqu'elle était donnée avant l'infection expérimentale et poursuivie pendant dix semaines seluement après l'inoculation d'épreuve, s'est montreé suffisante pour prévenir la mortalité par tuberculose, pendant au moins les vingt-six semaines de l'observation, et pour obtenir l'augmentation pondérale des cobayes, dans les mêmes proportion que le cobaye normal non traité et non infecté. (*2*) Il apparait également qu'á la suite d'une infection tuberculeuse traitée par l'isoniazide, la réaction des cobayes réagissent à l'inoculation tuberculeuse ultérieure non traitée est très sensiblement la même que celle qu'ils présentent après la vaccination par le BCG.

Acknowledgment

Recognition is due the entire laboratory staff, whose work made this study possible. The size of the experimental population alone created many problems in management and animal care which were substantially increased by the necessity to carry out each operation in a specified manner, not necessarily the most straightforward or easiest, in order to ensure comparability of the experimental groups and to eliminate bias. Helen Gertz was in over-all charge of the laboratory operations, Lillian Lang carried out the tuberculin testing procedures, Beatrice Swanson was responsible for the bacteriologic work, Louise Hopwood served as the project statistician, and Forrest Cross assisted in solving innumerable technical and administrative problems.

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BRONCHOLITHIASIS[1, 2]

A Review of Twenty-Seven Cases

LAURENCE K. GROVES AND DONALD B. EFFLER

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INTRODUCTION

If lymph nodes which lie adjacent to the tracheobronchial tree calcify, they become inert, endogenous "foreign bodies" in an environment of constant motion, with a tendency to erode the wall of an adjacent bronchus and to enter the lumen. This sequence results in broncholithiasis, the surgical treatment of which often is fraught with hazards. This paper presents a review of the experience with 27 cases of broncholithiasis seen between 1949 and 1954. It is believed that most of the manifestations of the disease are represented among these cases as well as many problems of its therapy. The 27 patients represent essentially all patients operated upon for the condition and several interesting or problematical cases of patients not operated upon. A number of patients who have had only diagnostic bronchoscopy have not been included in the present report.

ETIOLOGY

Calcifications related to the lung parenchyma or to the tracheobronchial tree are extremely common roentgenographic findings. The parenchymal calcifications almost invariably represent the end-stage of healing of granulomatous pulmonary disease. In contrast, the calcifications adjacent to the major branches of the tracheobronchial tree represent the end-stage of any one of many types of lymphadenitis. Identifying histologic or bacteriologic features usually have disappeared by the time calcification has occurred.

Histoplasmosis appears to be of prime etiologic importance in cases reported from the eastern central United States (1, 2). Other fungal diseases and tuberculosis are also significant factors. Lymph nodes that drain areas of any type of chronic pulmonary suppuration may become calcified during the healing process. In the Cleveland area, calcifications are seen in approximately 50 per cent of all routine roentgenograms of the chest; this incidence undoubtedly would be higher if oblique and Bucky films also were routinely taken (figure 1). Radiolucent anthracotic lymph nodes also may behave as broncholiths. Fortunately, the etiology of broncholithiasis rarely is of importance. The calcified node represents the "tombstone" of the original disease and, as such, forms the mechanical basis for a new and unrelated disease process.

[1] From the Department of Thoracic Surgery, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

[2] Presented before the Medical Session, as part of *Section 4A*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 24, 1955.

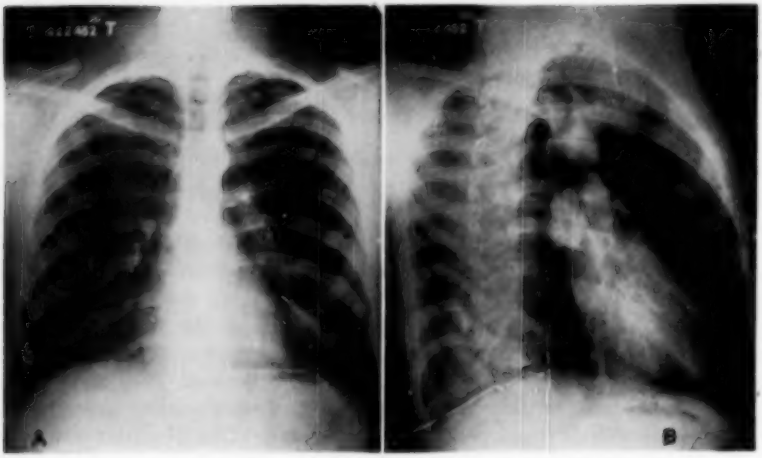

FIG. 1 (*A* and *B*). Roentgenograms clearly demonstrating how extensive calcifications may be overlooked on the routine postero-anterior view. Oblique and lateral films may be extremely helpful. The calcified mass was readily resected from beneath the carina.

TABLE 1

INCIDENCE OF SYMPTOMS IN 27 CASES OF BRONCHOLITHIASIS

Symptom	Number of Cases
Hemoptysis	17
Cough	16
Fever	6
Wheeze or "asthma"	6
Dyspnea	3
Chest pain	2
Coughed-up "stones"	2
Weight loss	2

SYMPTOMATOLOGY

The symptoms noted in the present series of 27 patients are summarized in table 1. They can be readily grouped into three major categories: *bleeding*, *cough*, and *bronchial obstruction*.

In any particular patient the symptomatology associated with the eroding broncholith varies considerably with its location and the degree of penetration. A peripheral calcification, situated beyond the area of cough reflex and too distal to cause significant obstructive pneumonitis, may be evidenced only by recurrent hemoptysis. This situation is unusual, however, and only 2 patients in the group had bleeding from peripheral calcifications. Erosions which occur in the major ramifications of the tracheobronchial tree ordinarily will cause hemoptysis and harrassing cough as initial symptoms. These symptoms are

comparable with those seen in other forms of endobronchial disease or in the presence of an endobronchial foreign body.

In the present group of patients, as is shown in table 1, hemoptysis and cough each occurred in almost two-thirds of the patients. There were, however, several patients who denied having cough other than that directly associated with hemoptysis. It should be remembered that these calcifications may erode not only a bronchus, but also adjacent blood vessels; and, although hemoptysis frequently is only minor in nature, this is not necessarily the case.

Small calcified lesions may be totally extruded into the bronchus and expectorated. This history was given by only 2 patients in the group. It is of interest that 2 additional patients with free stones in the tracheobronchial tree which were removed bronchoscopically had never coughed up anything recognized as a stone. After removal of the stones, it was not possible to demonstrate any erosion or deformity of the tracheobronchial tree to suggest the site of origin of the stones in either of the patients. Other patients not included in the series have been encountered who said that they had coughed up stones, the sources of which could not be demonstrated roentgenographically or bronchoscopically. Most of these histories undoubtedly are valid, but there is no objective means to prove the diagnosis.

As opposed to the small stone that is totally extruded, the portion of the usual broncholith appearing within the lumen is analogous to the portion of an iceberg which appears above the water. This type of broncholith may manifest its progress by a steadily increasing bronchial obstruction with associated wheezing respirations and localized obstructive emphysema. The final stage is that of total

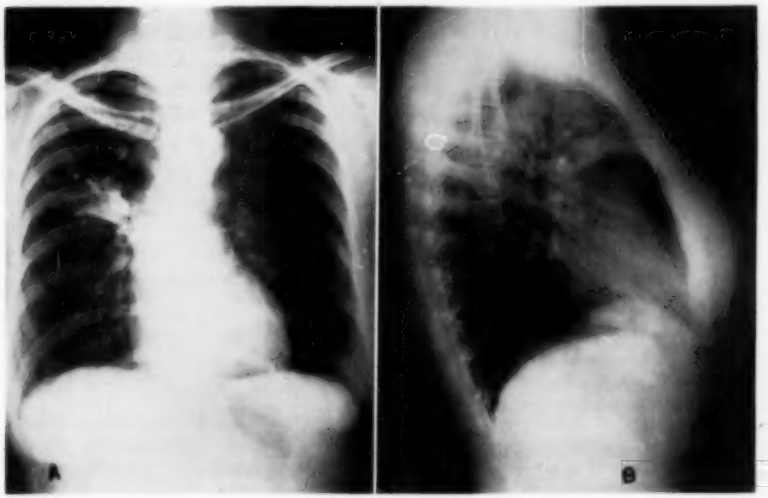

FIG. 2 (*A* and *B*). Roentgenograms clearly showing the segmental type of atelectasis which broncholithiasis may cause. The offending calcifications are well demonstrated.

bronchial obstruction with resultant obstructive pneumonitis, bronchiectasis, and contraction of pulmonary parenchyma distal to the lesion (figure 2). This chain of events readily accounts for the prevalence of the symptoms of fever, wheezing, dyspnea, and pain in the chest.

The symptoms discussed above are those that occur when a broncholith erodes in a person without other significant pulmonary disease. There is another large group of patients who have what might be called "complicated broncholithiasis" in which the calcified lymph nodes reflect the presence of chronic active pulmonary suppuration. These patients present the usual symptoms of their primary suppurative disease with frequently superimposed hemoptysis. If the disease is localized in such patients, the surgical indications usually are clear and the broncholiths become a problem chiefly at the time of operation when they complicate the hilar dissection.

DIFFERENTIAL DIAGNOSIS

As noted in table 2, which lists the pertinent roentgenographic findings in the present group of cases, obstructive pneumonitis is next to prominent calcifications in frequency. This is a difficult entity to define roentgenographically; however, a most important feature is persistence of the area of pneumonitis on repeated films. Such a persistent area of pneumonia, when associated with the prevalence of hemoptysis and cough, makes bronchogenic carcinoma the most significant diagnosis to be considered. Tuberculosis is the next most important consideration. Frequently this differentiation cannot be made until the time of thoracotomy because the lesion may be beyond the range of adequate bronchoscopic visualization or because the stone may be obscured by granulation tissue that bleeds readily on touch. Calcifications in the area of the lesion are of limited diagnostic significance because their common occurrence tends to preclude preoperative recognition of their true significance. Although prominent calcifications were mentioned in the roentgenographic reports of 16 of these patients, the same reports suggested bronchiolithiasis as the etiologic diagnosis in only 2 instances. Undoubtedly, more frequent use of laminagrams would increase the accuracy of roentgenographic diagnosis; but this would be chiefly of academic value since the treatment of the lesion remains surgical.

TABLE 2

ROENTGENOGRAPHIC FINDINGS IN 27 CASES OF BRONCHOLITHIASIS

Roentgenographic Finding	Number of Roentgenograms
Prominent calcifications	16
Obstructive pneumonitis or local infiltration	11
Bronchiectasis (bronchogram)	4
Enlarged hilum	2
Broncholithiasis suggested as diagnosis	2
Emphysema	2
Empyema	1
Cavitation	1
Normal	1

TABLE 3

INCIDENCE OF CALCIFICATIONS ON 100 CONSECUTIVE CHEST ROENTGENOGRAMS

Diagnosis	Number of Roentgenograms
No calcifications	50
Hilar calcifications	34
Hilar and parenchymal calcifications	15
Parenchymal calcifications alone	1
Total	100

In a recent review of one hundred consecutive roentgenograms by the department of roentgenology, the incidence of calcifications was reported to be 50 per cent (table 3). One hundred cases represents a small series, but the frequency with which calcification is observed on the roentgenogram certainly offers good reason for the low accuracy of the roentgenographic recognition of broncholithiasis. On the other hand, the clinician has the great advantage of being able to correlate all the findings in any given case. Thus, although he cannot definitely disprove the presence of carcinoma, he frequently has enough evidence to cause him to suspect that he is dealing with an inflammatory rather than a neoplastic process.

In a number of patients of the present series, the chief complaints were of an asthmatic nature although a diagnosis of typical bronchial asthma usually was excluded by careful questioning. This is mentioned to stress the importance

FIG. 3. *A*. Roentgenogram demonstrating prominent calcifications in the right hilum which was obtained while the patient was in a pre-symptomatic stage. *B*. Roentgenogram taken approximately a year later showing the infiltration in the right midlung field following six weeks of discomfort on the right side of the chest. At bronchoscopy the middle lobe bronchus was obstructed by a calcified lymph node. A difficult right upper and middle lobectomy was performed, dissection being complicated by the extensive calcifications. *M. tuberculosis* was cultured from the resected specimen.

TABLE 4

TREATMENT IN 27 CASES OF BRONCHOLITHIASIS

Procedure	Number of Cases	
Pulmonary resection		20
Lobectomy or bilobectomy	16	
Pneumonectomy	3	
Wedge resection	1	
Resection of calcification without pulmonary resection		1
Endoscopic removal		3
Endoscopic diagnosis only		3

of bronchoscopic examination in the evaluation of many types of chronic, supposedly nonsurgical, pulmonary disease.

Although tuberculosis undoubtedly is an important cause of stone formation, active pulmonary tuberculosis was proved in only 4 of these patients. In 3 of these 4 there was tuberculosis in the obstructed lung distal to the broncholiths (figure 3); the remaining patient with extensive subcarinal broncholithiasis subsequently died of pulmonary tuberculosis. The possibility of the presence of tuberculosis certainly must be considered in these patients; in only one patient, however, were difficulties encountered which might be attributed to early operation. Rarely does broncholithiasis simulate typical pulmonary tuberculosis. As the major concern in most of the diagnostic problems in the group was neoplasm, rather than tuberculosis, prolonged preoperative preparation was precluded.

TREATMENT

The types of treatment utilized in the group of cases are enumerated in table 4. The most common situation requiring treatment in this disease is the destruction of bronchial integrity by the eroding stone, with associated obstructive pneumonitis and its sequelae in the distal lung. Under these circumstances, the only treatment that ordinarily is practicable is resection of the involved portion of the bronchial tree. Pulmonary resection was performed in 20 of the 27 cases of the present series. In the writers' experience this disease presented many technical difficulties at the time of resection. Tissue planes and anatomical land marks almost invariably have been destroyed; the primary bronchi and related pulmonary vessels may be fused by the inflammatory process; and the prolonged operating time and the increased blood loss may become significant factors.

Lobectomy or bilobectomy was performed in 16 patients. This is definitive and at the same time nondisabling surgery; there was no mortality in this group. Almost all of the patients in whom the results are excellent are in this group.

In the writers' experience, segmental resection procedures are rarely suitable for treating this disease, because the most common site for bronchial erosion is at the level of division of the lobar into segmental bronchi. In only one case was a lesser resection than lobectomy performed. It is interesting that in 7 of the 16 cases the middle lobe was included in the resection. Lymph node com-

FIG. 4. Lateral roentgenogram showing the classic picture of a contracted airless right middle lobe. The hilar structures in this patient were so markedly involved with calcified lymph nodes that a first attempt at middle lobectomy was abandoned; lobectomy was completed a year later.

pression of the bronchus plays an important role in the middle lobe syndrome, and broncholithiasis is a common finding late in middle lobe disease (figure 4).

Pneumonectomy was performed in 3 instances and 2 of these procedures resulted in postoperative deaths. These 2 deaths well exemplify some of the difficulties encountered and will be very briefly summarized.

A 61-year-old woman had been aware of progressive cough and associated dyspnea with a loud right-sided wheeze for nine months. Chest roentgenogram (figure 5A) showed a partially collapsed right upper lobe with prominent calcifications in the right hilum and the right paratracheal region. At bronchoscopy the right main bronchus at the level of the carina was almost totally occluded by calcareous matter and granulation tissue. A right pneumonectomy was performed. This was an extremely difficult procedure because the calcifications adhered to the main pulmonary artery and the integrity of the terminal trachea had been destroyed by the eroding disease. The bronchial stump closure was precarious and was reinforced with a pedicle flap of pericardial fat. This patient disrupted her bronchial stump thirty days postoperatively and, in spite of open drainage, she died several days later. Pathologic examination disclosed tuberculosis in the right upper lobe, which might possibly be a significant finding in this case in regard to the late leak in the bronchial stump.

The eroding broncholith in this case represented a calcification at the site of the azygous lymph node. In all probability this lesion at one stage represented a paratracheal granuloma and the course in this particular instance offers a sound argument for surgical treatment of these lesions.

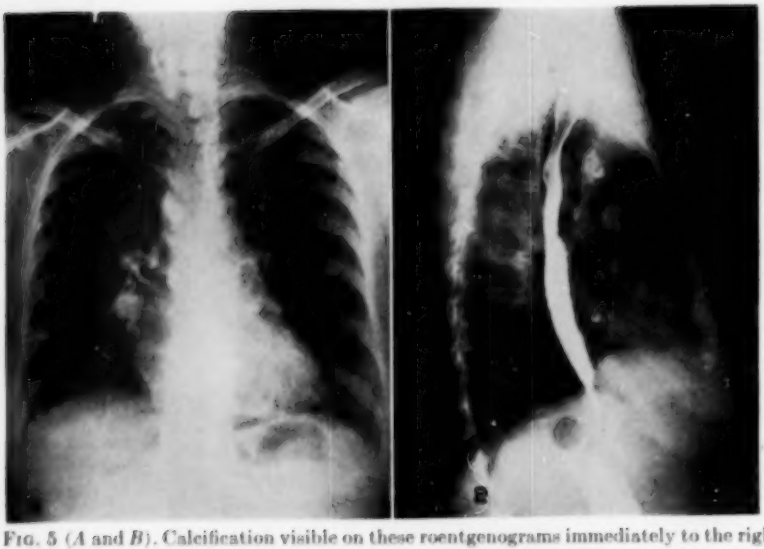

FIG. 5 (*A* and *B*). Calcification visible on these roentgenograms immediately to the right of and anterior to the trachea, just above the carina, virtually destroyed the integrity of the right main bronchus. Note the elevation of the short fissure of the right lung and infiltration in the right upper lobe. Following pneumonectomy, tuberculosis was demonstrated in the right upper lobe.

A 40-year-old man entered the hospital critically ill as a result of acute sepsis from a putrid right empyema; the empyema was drained (figure 6*A*, *B*, and *C*). He had been seen previously because of other conditions, at which time a routine chest roentgenogram had shown extensive calcifications in the right hilar region. The significance of these calcifications was not recognized until approximately a month following drainage when evaluation was undertaken to ascertain the cause of the empyema. Bronchoscopic examination demonstrated that the right middle lobe bronchus was completely occluded by a calcification. Undoubtedly the empyema occurred secondary to obstructive pneumonitis in the right middle lobe. Although there was a large chronic empyema cavity present, it was believed that pulmonary resection was the only possible definitive therapy. At the time of surgery extensive disease in the hilar portion of the lung proper made pneumonectomy the only feasible procedure and, although the pericardium had to be opened, pneumonectomy was performed without incident. The patient subsequently died of septic pericarditis.

The remaining 7 patients did not undergo pulmonary resection. One, a 76-year-old man with segmental atelectasis in the right upper lobe, was found at bronchoscopy to have an anthracotic nodule compromising the right upper lobe bronchus. There was no evidence of neoplasm on cytologic or biopsy study, and he was believed to be an unsuitable surgical candidate.

In another patient, a diagnosis of tracheopathia osteoplastica (3) was established by bronchoscopy. The patient had multiple polypoid lesions containing actual bone on biopsy. This condition does not warrant further discussion here, but is mentioned for completeness. No adequate treatment for this entity is known.

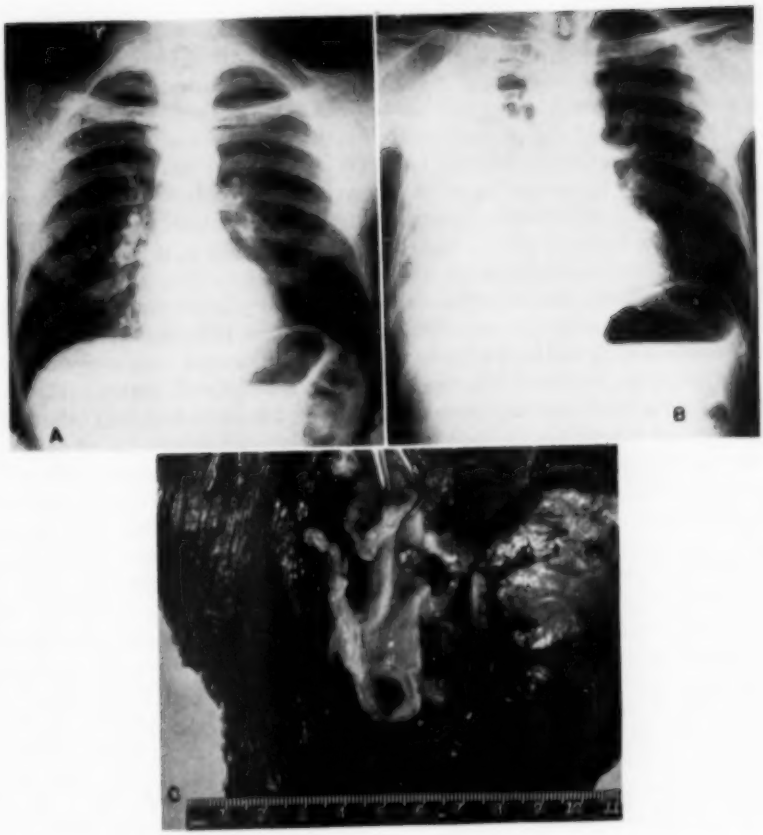

FIG. 6. *A*. Note the calcifications adjacent to the right hilum in this otherwise normal chest roentgenogram. The patient at this time had no chest symptoms. *B*. This roentgenogram was obtained two years after that shown in *A*. The patient was acutely ill with an unexplained putrid empyema. *C*. Photograph of the opened bronchial tree following right pneumonectomy. The right middle lobe bronchus was totally occluded by the calcifications apparent in the opened lumen.

A third patient with repeated episodes of chills and fever associated with productive cough was found at bronchoscopy to have a markedly widened carina with small ulcerations just below the carina on the medial wall of each bronchus which exuded large amounts of creamy pus. It is believed that, while this lesion represents breakdown of a mediastinal granuloma (4), it nevertheless represents a stage in the development of broncholithiasis. Bacteriologic study of the pus was nonrevealing and, in view of absence of response to antituberculous therapy, it has been recommended that a resection of the lesion with plastic closure of the two bronchial defects be attempted.

A later stage of this same process was presumably represented in the case of a 71-year-old man who had a harassing moderately productive cough of one and one-half years' duration. A large group of calcified subcarinal lymph nodes was roentgenographically visible, and at bronchoscopy these lymph nodes were seen to have eroded the medial walls of both main bronchi. The patient was bronchoscoped on three occasions; however, the material was in one solid mass and too hard to be broken up with any available bronchoscopic instruments. He died of active tuberculosis approximately three years after the last examination. It is now believed that in cases of this type resection of the broncholiths with a plastic bronchial closure should be attempted.

A 30-year-old man subsequently was seen with an extensive group of calcified subcarinal lymph nodes and a ten-year history of minor hemoptysis (*see* figure 1). The bronchoscopist saw a small ulceration below the carina on the medial wall of the right main bronchus. The large mass of calcified lymph nodes was readily removed through a right thoracotomy; however, the bronchial tree bilaterally seemed to be intact. This patient subsequently has had several minor episodes of hemoptysis, and bronchograms have demonstrated a subsegment with bronchiectasis in the right lower lobe which is believed to be the source of bleeding. Nevertheless, it is believed that this approach to the problem of broncholithiasis should be given careful consideration as a prophylactic measure. Certainly the procedure is simple when compared with that necessary in the more complicated cases already cited.

Two additional patients have had bronchoscopic removal of broncholiths lying free within the major bronchi, following which there have been no recurrence of wheezing and coughing and no demonstrable erosions within the bronchial tree.

DISCUSSION

In this series of 27 cases there have been 2 minor postoperative empyemas and 2 fatal complications. The results are summarized in table 5. As has been mentioned, when the involved portions of the tracheobronchial tree and lung distal thereto are resectable, the postoperative results are highly satisfactory. In several patients who had resections, preoperative roentgenograms demonstrated rather extensive calcifications elsewhere, including the opposite side. Thus far,

TABLE 5

FOLLOW-UP IN 27 CASES OF BRONCHOLITHIASIS

Postoperative results		Number of Cases
Excellent (no respiratory symptoms)		16
Good		4
Some persistent cough	3	
Minor hemoptysis	1	
Death		2
No definitive therapy		4
Lost to follow-up		1

TABLE 6

FINDINGS IN 27 CASES OF BRONCHOLITHIASIS

Factor	Range	Average
Age of patient	29 through 76 years	53.5 years
Duration of symptoms	1 month through 35 years (hemoptysis)	4.5 years

the writers have not been confronted with the problem of broncholithiasis subsequently occurring in the opposite lung.

The therapeutic problems in this disease become compounded as the offending broncholiths occur more proximally in the tracheobronchial tree. To date the treatment of broncholiths in subcarinal and paratracheal positions has not been satisfactory. A more aggressive surgical treatment of these lesions is contemplated for the future and it is believed that there is a definite place for prophylactic surgery for major calcifications in these locations. Certainly, early symptomatology, such as an irritating cough with the finding of major calcifications adjacent to the proximal tracheobronchial tree, warrants serious consideration of surgical removal of the calcifications. Undoubtedly, many of these lesions have passed through the stage of mediastinal granuloma, and it seems to the writers that the possibility of subsequent difficulty with mediastinal granuloma warrants their surgical removal or evacuation (4). Not only may these lesions cause tracheal difficulties, but it is well recognized that they may cause superior vena caval obstruction, which is a further argument for treating them surgically.

In view of the great frequency of roentgenographically visible calcified lesions, the incidence of clinically significant broncholithiasis must be extremely small. There is no apparent means of predicting which patient will develop broncholithiasis. Certainly a patient with major central calcifications should be kept under surveillance and any symptoms in the lower respiratory tract should be considered a strong indication for bronchoscopic examination. An awareness of this condition and a high index of suspicion will certainly increase the likelihood of an early diagnosis and successful treatment. Although broncholithiasis tends to be a disease of older people, the average age being 53.5 years in this series, one patient was 29 years old (table 6). In this series, the average duration of symptoms was 4.5 years, and there seems to be no question that the technical aspects of treatment would be much simpler if the disease were treated earlier in its course.

SUMMARY

Compared with the high incidence of calcifications associated with the lower respiratory tract, the incidence of clinically significant broncholithiasis is low. However, it is a significant cause of pulmonary disease necessitating major surgery and frequently it masquerades as pulmonary neoplasm. An awareness of the possibility of the condition, with resultant increased diagnostic suspicion and increased use of the bronchoscope, should lead to more frequent and earlier diagnosis. Although this is a benign condition, its late complications may be

virtually untreatable. Based on the present experience with 27 cases, it is believed that an aggressive therapeutic approach is warranted in the earlier phases of the disease.

SUMARIO

Broncolitiasis. Repaso de Veintisiete Casos

Comparado con la incidencia de calcificaciones vinculadas con la porción inferior del aparato respiratorio, la incidencia de broncolitiasis clínicamente importante es baja. No obstante, constituye una causa importante de neumopatía que exige cirugía de orden mayor y frecuentemente se disfraza como neoplasia pulmonar. El conocimiento de la posibilidad de la dolencia, con el consiguiente aumento de la suspicacia diagnóstica y el mayor uso del broncoscopio, debe conducir al diagnóstico más frecuente y más temprano. Aunque se trata de una dolencia benigna, las complicaciones tardías tal vez sean virtualmente intratables. A base de la reciente observación de 27 casos, parece que en las fases incipientes de la enfermedad, está justificado un aborde terapéutico atrevido.

RESUME

Broncholithiase. Analyse de vingt-sept cas

Par comparaison avec l'incidence élevée des calcifications associées aux lésions des voies respiratoires inférieures, l'incidence de la broncholithiase, significative du point de vue clinique, est basse. Toutefois, elle constitue une cause appreciable de maladie pulmonaire nécessitant l'intervention chirurgicale majeure; elle prend fréquemment le masque d'un néoplasme pulmonaire. La connaissance de la possibilité de cette affection entraînant une plus fréquente suspicion quant à ce diagnostic et l'emploi plus fréquent du bronchoscope devraient augmenter la frequence et la précocité de ce diagnostic. Bien que ceci soit une affection bénigne, ses complications tardives sont parfois virtuellement intraitables. Basés sur l'expérience actuelle portant sur 27 cas, les auteurs sont d'avis qu'un abord thérapeutique agressif est justifié durant la phase précoce de l'affection.

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REACTIVATION OF INACTIVE PULMONARY TUBERCULOSIS[1]

JULIUS KATZ, SOLOMON KUNOFSKY, AND BEN LOCKE

(Received for publication May 20, 1955)

INTRODUCTION

Information regarding the frequency with which inactive pulmonary tuberculosis becomes reactivated is of practical importance not only to the clinician, but also to those responsible for the follow-up of persons found with inactive disease in roentgenographic surveys and to those interested in the employment or rehabilitation of the tuberculous. This is a report of a study to determine the frequency with which reactivation occurs and to analyze some of the factors involved.

MATERIALS AND METHODS

The subject of this study is a group of mental patients who were found to have pulmonary tuberculosis during the conduct of a tuberculosis control program in the eighteen mental hospitals of the New York State Department of Mental Hygiene. The period covered in this report extended from 1941 through 1952; the maximum period of observation was twelve years.

This study was at first an attempt to determine how often reactivation occurs, and the effect of time upon the reactivation rate. For this purpose, the records were reviewed of 1,532 patients whose tuberculosis became inactive during their stay in mental hospitals. These patients were under observation during the time when their disease changed from an active to an inactive status, so that the duration of the period of inactivity was known. The maximum period of observation of this group was nine years. These patients are referred to as cases of "new" inactive tuberculosis.

For comparative purposes, a group of 7,105 patients was studied who were admitted to mental hospitals with inactive tuberculosis or were found to have inactive disease at the time of the initial chest roentgenographic surveys of each institution which were conducted at the beginning of the control program. The duration of the inactive status of the tuberculous disease of these patients prior to the first roentgenogram was unknown, and they are referred to as cases of "old" inactive disease. The date of their initial chest roentgenograms was taken at the starting point of their period of observation. This group was followed for a maximum period of twelve years, but for comparison with the "new" cases, only the first nine years are considered in this report.

The life-table method was used to determine the reactivation rates for both groups in tables 2 and 3.

Study of these two groups indicated that, in addition to time, the effect of exposure to infectious tuberculosis after the disease becomes inactive must also be considered.

[1] From the Division of Tuberculosis Control, Department of Health, State of New York.

In the hospitals concerned, patients with active or arrested disease were kept on tuberculosis wards. When the disease became inactive, the patients might or might not have been transferred from these wards, depending upon the need for beds for patients with active disease. The decision to transfer or not to transfer these patients from the tuberculosis wards was purely an administrative one, based upon the bed requirements. Segregation of patients with roentgenographic evidence of inactive tuberculosis in the initial survey or upon admission to mental hospitals was also decided upon the same administrative grounds, but these patients were less apt to be housed on the tuberculosis wards. As the number of patients with active or arrested disease has been decreasing during the past several years, many patients remained for a considerable period of time on the tuberculosis wards after their disease was considered inactive. On these wards, patients known to have infectious sputum were usually kept separate from those with noninfectious sputum, but contact between the two groups was not entirely eliminated. Those with inactive disease who remained on these wards were therefore subject to more exposure to infectious tuberculosis than patients removed from these wards when their disease became inactive. The relative risk of reactivation in the two groups was studied.

At the beginning of the tuberculosis control program, it was the practice in most of the hospitals to segregate known cases of tuberculosis in special wards. In accordance with the policy of concentrating all tuberculous patients in a few institutions, most of the hospitals gradually discontinued tuberculosis wards. Their tuberculous patients were sent to three centers for the care of this type of patient. Except for two hospitals, information was not available as to which patients with inactive tuberculosis were residents on the tuberculosis wards and which on the general wards during each year of this study, but the total number of such patients in each institution was known. Also, the number of hospitals with and without tuberculosis wards was known for each year. Accordingly, the hospitals were divided into two groups, those with and those without tuberculosis wards, and the reactivation rates were compared.

In two hospitals with separate tuberculosis wards, the Hudson River and the Pilgrim state hospitals, information was available regarding the number of patients with inactive tuberculosis by ward residence. For Pilgrim, reactivation rates of the tuberculosis division of the hospital (Edgewood) for the four-year period 1950 through 1953 were compared with those of the rest of the institution. For Hudson River, rates were obtained for a period of slightly more than ten years, from 1943 to 1953, for patients who were residents on the tuberculosis wards, on the general wards, and in several cottages housing patients with inactive tuberculosis.

Definition of Terms

The term *inactive* can accurately be applied only to those lesions which reached a condition of inactivity as defined in the 1950 edition of the *Diagnostic Standards*, published by the National Tuberculosis Association, or of apparently cured as defined in the 1940 edition. The criteria set forth in these standards include stable or slowly shrinking lesions as observed in serial roentgenograms, the absence of symptoms, and the absence of tubercle bacilli in the sputum or gastric contents. Unfortunately, in the case of the patients included in the present study, these criteria could not be applied as closely as is recommended in the *Diagnostic Standards*. Due to the lack of cooperation of the patients, the presence or absence of symptoms was often difficult to determine. More important, due to limitation of laboratory facilities, studies of sputum or gastric contents at the recommended intervals often could not be performed. As a result, the determination of the clinical status of the disease was made chiefly from serial chest roentgenograms. In order to compensate as much as possible for the frequent absence of adequate laboratory data, the periods of roentgenographic observation of these patients were quite long. For those whose disease was active or arrested at some time during their stay within the institution, a minimum period of two years without change in the roentgenographic appearance of the lesion was used before the disease was considered inactive. In many cases, the period was considerably longer.

The finding of tubercle bacilli in the sputum or gastric contents or any increase in the extent of disease as shown in the roentgenogram was considered evidence of reactivation.

The treatment of active tuberculosis among these patients consisted mainly of bed rest, with use of collapse therapy and surgery occasionally. During the past few years antimicrobial therapy has been employed to an increasing extent, though few received such therapy before 1950.

RESULTS

Total reactivation rates: For the entire group the average annual reactivation rate was 2 per cent (table 1). The rate of 2.6 among "new" cases of inactive disease was 73 per cent higher than the rate of 1.5 among the "old" cases (table 2). This difference was statistically significant.

TABLE 1

REACTIVATION OF INACTIVE TUBERCULOSIS BY TYPE OF HOSPITAL (WITH OR WITHOUT TUBERCULOSIS WARDS), 1944–1952

Period	Hospitals With Tuberculosis Wards			Hospitals Without Tuberculosis Wards			Total		
	Person-Years	Reactivation		Person-Years	Reactivation		Person-Years	Reactivation	
		Number	Rate per 100 Person-Years		Number	Rate per 100 Person-Years		Number	Rate per 100 Person-Years
1944–1946	9,528	237	2.5	3,856	51	1.3	13,384	288	2.2
1947–1949	9,630	206	2.1	3,813	60	1.6	13,443	266	2.0
1950–1952	8,362	197	2.4	5,684	80	1.4	14,046	277	2.0
1944–1952	27,520	640	2.3*	13,353	191	1.4*	40,873	831	2.0

* Probability of the difference in rates being due to chance is less than 0.000001.

TABLE 2

REACTIVATION OF INACTIVE TUBERCULOSIS BY SEX AND BY PERIOD AFTER CLASSIFICATION AS INACTIVE, FOR "NEW" AND "OLD" CASES

Period After Classification as Inactive	Both Sexes			Males			Females		
	Person-Years	Reactivation		Person-Years	Reactivation		Person-Years	Reactivation	
		Number	Rate per 100 Person-Years		Number	Rate per 100 Person-Years		Number	Rate per 100 Person-Years
"New" cases									
Total	6,734	178	2.6*	3,311	118	3.6	3,423	60	1.8
0–3	4,132	120	2.9	2,040	80	3.9	2,092	40	1.9
3–6	2,109	50	2.4	1,007	32	3.2	1,102	18	1.6
6–9	493	8	1.6	264	6	2.3	229	2	0.9
"Old" cases									
Total	38,099	558	1.5*	19,947	333	1.7	18,152	225	1.2
0–3	18,358	234	1.3	9,623	133	1.4	8,735	101	1.2
3–6	11,443	215	1.9	6,002	129	2.1	5,441	86	1.6
6–9	8,298	109	1.3	4,322	71	1.6	3,976	38	1.0

* Probability of this or greater difference being due to chance is less than 0.000001.

TABLE 3

REACTIVATION OF INACTIVE TUBERCULOSIS BY AGE AND PERIOD AFTER CLASSIFICATION AS INACTIVE, FOR "NEW" AND "OLD" CASES*

Period After Classification as Inactive	Less Than Forty-Five Years			Forty-Five Years and Older		
	Person-Years	Reactivation		Person-Years	Reactivation	
		Number	Rate per 100 Person-Years		Number	Rate per 100 Person-Years
"New" cases						
Total	1,890	62	3.3†	4,816	115	2.4†
0–3	1,182	46	3.9	2,927	73	2.5
3–6	588	15	2.6	1,516	35	2.3
6–9	120	1	0.8	373	7	1.9
"Old" cases						
Total	8,879	137	1.5	29,220	421	1.4
0–3	3,933	52	1.3	14,425	182	1.3
3–6	2,769	58	2.1	8,674	157	1.8
6–9	2,177	27	1.2	6,121	82	1.3

* Difference between data in tables 2 and 3 is due to inclusion of patients with age not stated in table 2.

† Probability of difference between age groups among "new" patients being due to chance is less than 0.05.

Reactivation by sex: Males had higher reactivation rates. For "new" cases the rate was twice as high as for females (3.6 and 1.8); for "old" ones, it was approximately 40 per cent greater (1.7 and 1.2) (table 2). This was also statistically significant.

Reactivation by age: Patients under forty-five years had somewhat higher reactivation rates than older patients (table 3). The difference was not significant for "old" cases; for "new" cases the probability that this difference occurred by chance was less than 0.05.

Reactivation by stage of disease prior to reaching inactive status: There was a higher reactivation rate among patients whose disease was advanced at the time of inactivation. The difference between minimal and advanced cases among males was statistically significant. Among females those with minimal disease showed a higher reactivation rate, but the difference was not significant (table 4). These data are for "new" cases only since the original status of "old" cases is unknown.

Reactivation by time after reaching inactive status: Among "new" cases the reactivation rates decreased with the passage of time, although the differences were not statistically significant. "Old" cases did not show this downward trend during the same period (table 2), although subsequent data, not shown in the table, indicated a decrease in reactivation rate with time among these patients also.

Effect of differences in exposure to infectious tuberculosis (wards of residence): As mentioned above, grouping of all patients with inactive tuberculosis by residence in tuberculosis or in general wards was not possible except for two hos-

TABLE 4

REACTIVATION OF INACTIVE TUBERCULOSIS BY SEX AND STAGE OF DISEASE BEFORE INACTIVATION, FOR "NEW" CASES

	Stage of Disease					
	Minimal			Moderately and Far Advanced		
	Person-Years	Reactivation		Person-Years	Reactivation	
		Number	Rate per 100 Person-Years		Number	Rate per 100 Person-Years
Both sexes	5,580	139	2.5	1,154	39	3.4
Males	2,788	88	3.2*	523	30	5.7*
Females	2,792	51	1.8	631	9	1.4

* Probability of such difference (or greater) being due to chance is less than 0.01.

pitals. All hospitals were therefore divided into those with and those without tuberculosis wards, and reactivation rates were compared upon the assumption that, if rates were higher among patients on the tuberculosis wards, they would tend to raise the rates for the entire hospital in which they were located.

As shown in table 1, the reactivation rate in hospitals with tuberculosis wards (2.3) was 64 per cent greater than in those without such wards (1.4). This was true for males and females separately, and for every year of the nine-year period 1944–1952, although for the sake of brevity the rates are given for three-year intervals.

Since it is shown in table 1 that patients in hospitals with tuberculosis wards have higher reactivation rates, while in table 2 is shown that "new" cases have higher rates than "old", the possibility was considered that the higher rates in hospitals with tuberculosis wards might be due to a higher proportion of "new" cases. It was found, however, that, even if all "new" cases were assumed to be residents on the tuberculosis wards and were removed from consideration, there was still a very high statistically significant difference in reactivation rates between hospitals with and hospitals without tuberculosis wards.

Exposure and reactivation in the two hospitals with tuberculosis and nontuberculosis wards: The association of exposure and reactivation was further demonstrated by the results obtained in the two hospitals where direct comparison was possible between rates among patients on the tuberculosis wards and those in the other wards of the institutions, i.e., the Hudson River and the Pilgrim state hospitals.

At the Hudson River State Hospital, patients with inactive tuberculosis were housed on the tuberculosis wards, where exposure to infectious tuberculosis was greatest; on the general wards of the institution, where exposure was least; and in cottages containing mainly patients with inactive tuberculosis, where exposure was probably intermediate. As shown in table 5, reactivation rates were more than twice as high among residents on the tuberculosis wards as among those on the general wards, while the rates among cottage residents were intermediate between the other two. These differences were statistically significant and were true for both males and females, and by age groups.

TABLE 5

REACTIVATION OF INACTIVE TUBERCULOSIS AMONG PATIENTS IN HUDSON RIVER AND PILGRIM STATE HOSPITALS BY SEX AND TYPE OF WARD

Sex and Type of Ward	Hudson River			Pilgrim		
	Person-Years	Reactivations		Person-Years	Reactivations	
		Number	Rate per 100 Person-Years		Number	Rate per 100 Person-Years
All patients—total	3,917	89	2.3	2,721	67	2.5
Nontuberculosis wards	2,288	41	1.8*	1,697	15	0.9†
Cottages	997	22	2.2	—	—	—
Tuberculosis wards	632	26	4.1*	1,024	52	5.1†
Males—total	1,823	51	2.8	1,365	37	2.7
Nontuberculosis wards	1,112	25	2.2	953	9	0.9
Cottages	507	13	2.6	—	—	—
Tuberculosis wards	204	13	6.4	412	28	6.8
Females—total	2,094	38	1.8	1,356	30	2.2
Nontuberculosis wards	1,176	16	1.4	744	6	0.8
Cottages	490	9	1.8	—	—	—
Tuberculosis wards	428	13	3.0	612	24	3.9

* Probability of this difference being due to chance is less than 0.001.

† Probability of this difference being due to chance is less than 0.000001.

TABLE 6

REACTIVATION OF INACTIVE TUBERCULOSIS AMONG PATIENTS IN HUDSON RIVER AND PILGRIM STATE HOSPITALS ON TUBERCULOSIS WARDS AND NONTUBERCULOSIS WARDS, FOR "OLD" AND "NEW" CASES

Type of Patients	Tuberculosis Wards			Nontuberculosis Wards		
	Person-Years	Reactivation		Person-Years	Reactivation	
		Number	Rate per 100 Person-Years		Number	Rate per 100 Person-Years
"New" patients	1,521	75	4.9	265	8	3.0
"Old" patients	880	25	2.8	3,972	48	1.2
All patients	2,401	100	4.0*	4,237	56	1.3*

* Probability of the difference being due to chance is less than 0.001.

In the Pilgrim State Hospital, reactivation rates were more than five times as high among patients in Edgewood, the tuberculosis division of the institution, as among those in the rest of the hospital (table 5). This difference was also statistically significant and held for both sexes.

For both hospitals the reactivation rates were higher among patients on the tuberculosis wards regardless of whether they were "new" or "old" (table 6). The differences were statistically significant for "old" cases, and for "old" and "new" cases taken together.

DISCUSSION

From the present study it appears that, even when exposure to infectious tuberculosis is minimal, the frequency of reactivation of inactive tuberculosis is

greater than the development of new tuberculosis by previously nontuberculous patients. This was shown by the fact that the incidence of tuberculosis among patients on the general wards of mental hospitals during the period of this report was approximately 0.4 per cent annually (1), while the reactivation rate among patients with inactive tuberculosis on these same wards was 1.4 per cent, or three times as great. The difference may be due to several factors:

> The first factor presumably is the difficulty in recognizing when tuberculosis is inactive, particularly in the absence of adequate laboratory study of sputum or gastric contents. Undoubtedly, some of the patients included in this report who were considered to have inactive tuberculosis had lesions which were not completely inactive, so that the so-called "reactivation" was actually an exacerbation of sluggishly active disease.
>
> Even when all of the criteria are met for the clinical classification of a lesion as inactive, the disease may nevertheless be pathologically active. The studies of Medlar (2), for example, show the existence of caseous areas in the lungs even though the sputum is noninfectious and the roentgenographic appearance of the disease suggests inactivity. The emergence of clinically active disease in these patients may also represent an endogenous exacerbation of a lesion of this type.
>
> Even when the tuberculous disease is completely healed clinically and pathologically, these patients are probably as subject to the subsequent development of tuberculosis following exposure (true reinfection) as patients who have never had tuberculosis.

The above factors may explain the difference between the rate of development of new cases of tuberculosis and the breakdown of inactive lesions under similar environmental conditions. While this report is concerned with the "reactivation of inactive tuberculosis," the patients studied undoubdtedly developed manifestly active disease from the sources described, although the relative frequency of each cannot be determined.

In studying the effect of exposure upon cases of inactive tuberculosis, the only known difference between the patients who remained on the tuberculosis wards after their disease had become inactive and those transferred to other wards was that of environment, i.e., differences in the duration of exposure to known cases of infectious tuberculosis. Since the criteria for the classification of pulmonary tuberculosis as inactive, crude though they may be, were the same for both groups, it may be concluded that the higher reactivation rates among those with longer periods of residence on the tuberculosis wards were due to the greater degree of exposure, even though the exact mechanism of the reactivation is unknown.

Because of the abnormal environmental conditions presented by the long period of hospitalization of the patients included in this study, the actual rates obtained cannot be applied to mentally sound tuberculous patients. However, since there is evidence that the reaction to tuberculosis of mental patients is inherently no different from that of sane persons (3), it is probable that the general observations regarding the importance of time, sex, age, stage of disease, and the effect of continued exposure are applicable to tuberculous patients as a whole.

The practical application of knowledge of the hazard of continued exposure must be considered in the light of its effect upon the segregation of tuberculous patients as well as upon the employment of persons with inactive tuberculosis.

The most obvious procedure to decrease this hazard to patients with inactive tuberculosis is to minimize their exposure to those with infectious disease. In tuberculosis hospitals where these two groups are not separated, such segregation should be instituted.

The claim is often made that persons who have recovered from tuberculosis have demonstrated resistance to this disease and may therefore be safely employed in tuberculosis hospitals. The opposite view may be taken that, if their resistance had been high, they would not have developed the disease at all. Regardless of the merits of each side of this argument, the evidence presented suggests a greater occupational hazard in the employment in tuberculosis hospitals of persons with inactive tuberculosis than in their employment where exposure to infectious tuberculosis is less. When they are accepted for employment in tuberculosis institutions, the need for care in their selection and in the conditions of their employment is readily apparent.

SUMMARY

A group of mental patients with inactive tuberculosis was studied to determine the frequency of reactivation, with particular attention to its relationship with time and with exposure to infectious tuberculosis.

For the group as a whole, the average annual reactivation rate was 2 per cent. Reactivation was more frequent among males and among patients less than forty-five years of age.

During the nine-year period of the study, no definite trend of reactivation with time was observed, although data available for a longer period show a decreasing trend.

Exposure of patients with inactive disease to cases of infectious tuberculosis apparently increases the probability of reactivation.

SUMARIO

Reactivación de la Tuberculosis Pulmonar Inactiva

Un grupo de psicópatas con tuberculosis inactiva fué estudiado para determinar la frecuencia de la reactivación, prestándose atención en particular a su relación con el tiempo transcurrido y con la exposición a tuberculosis infecciosa.

Para el grupo en conjunto, la tasa media de reactivación anual fué de dos por ciento. La reactivación fué más frecuente entre los varones y entre los enfermos de menos de cuarenta y cinco años.

Durante los nueve años del período de estudio, no se observó ninguna tendencia bien definida de reactivación en relación con el tiempo, aunque los datos disponibles para un período más prolongado muestran tendencia descendente.

La exposición de sujetos con enfermedad inactiva a casos de tuberculosis infecciosa acrecienta aparentemente las probabilidades de reactivación.

RESUME

Réactivation de la tuberculose pulmonaire inactive

Un groupe de malades mentaux atteints de tuberculose au repos a été étudié pour déterminer la fréquence de la réactivation en s'attachant particulièrement à ses rapports en

termes de temps et d'exposition à la tuberculose bacillifère. Pour le groupe dans son ensemble, le taux de réactivation moyen annuel était 2%. La réactivation était plus fréquente chez l'homme et chez les patients au-dessous de 45 ans.

Durant la période d'étude de neuf ans, il n'a été observé aucune tendance définie du taux de réactivation en rapport avec le temps, toutefois des données obtenues au cours une période plus longue montrent une tendance décroissante.

L'exposition des malades présentant la forme inactive de l'affection á la tuberculose avec expectoration bacillifère augmente visiblement le taux de probabilité de la réactivation.

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PULMONARY RESECTION IN MIDDLE-AGED AND ELDERLY PATIENTS[1, 2]

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INTRODUCTION

Most reports of pulmonary resection for tuberculosis make no special mention of the results in older patients. A few writers, such as Zelman and associates (1, 2) and Naef (3), stated that age per se had not contraindicated surgery in their series. Davidson and co-workers (4) presented some data for thirty patients aged fifty years or more at the time of operation. Twenty underwent pneumonectomy and ten lobectomy during the period from 1944 to 1952. The over-all death rate was 33.3 per cent and the frequency of bronchopleural fistula, 30 per cent.

The aim of the present investigation is to elucidate the possibilities of pulmonary resection for middle-aged and elderly tuberculous patients. The report is also intended to complement earlier reports on artificial pneumothorax and thoracoplasty in such patients (5, 6).

MATERIAL AND METHODS

The relative increase in pulmonary tuberculosis in middle-aged and elderly persons in Sweden is reflected in the rising proportion of sanatorium patients more than fifty years old. Thus, the percentage of tuberculous males in this age group admitted to Söderby Hospital rose from 8.3 in 1938 to 31.3 in 1954. The corresponding figures for older women were 1.3 and 12.2 per cent (figure 1). The total number of adult tuberculous patients admitted in 1938 was 786 and in 1954, 1,144. In calculating these figures deduction was made for readmission of discharged patients re-hospitalized in the same calendar year.

The present study comprises all of the patients fifty years of age or older who, during the period from November, 1949, to December, 1954, underwent pulmonary resection after sanatorium care at Söderby Hospital. To these 33 patients have been added 3 from Löt Sanatorium. Most of the operations were performed at the Surgical Department of Sabbatsberg Hospital, Stockholm. A few were carried out at Söderby Hospital and a few at the Thoracic Surgery Clinic in Lund. Prior to November, 1949, only one patient in this age group had been referred from Söderby or Löt for pulmonary resection. In this case lobectomy was performed in 1943 for suspected neoplasm.

OBSERVATIONS

General Background of the Operated Cases

The distribution of the clinical material according to age and sex is shown in table 1. The mean age at operation was 53.3 years for men; 56.5 for women; and

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[2] This investigation has been carried out with the aid of a grant from the Swedish National Association Against Tuberculosis.

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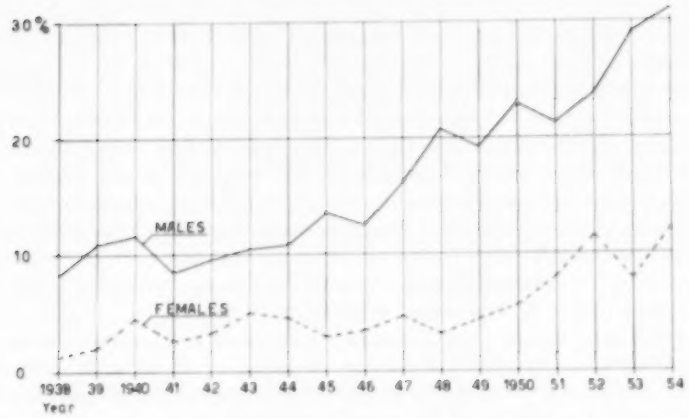

FIG. 1. Number of patients fifty years of age and older admitted each year (expressed as per cent of the total admissions of each sex).

TABLE 1

AGE OF PATIENTS AT TIME OF PULMONARY RESECTION

Age in Years	Males	Females	Total
50 to 54	17	6	23
55 to 59	7	3	10
60 to 64		3	3
Total	24	12	36

TABLE 2

PULMONARY RESECTION PROCEDURES IN PATIENTS MORE THAN FIFTY YEARS OF AGE

Age at Operation	Pneumonectomy	Lobectomy	Lobectomy Plus Segmental Resection	Segmental Resection	Total
years					
50 to 54	5	7	5	6	23
55 to 59	1	7		2	10
60 to 64	2	1			3
Total	8	15	5	8	36

for all patients, 54.3 years. The resection procedures employed are reported in table 2.

Two women and 2 men had diabetes. Five men had had gastric ulcer. In 4 of them partial gastric resection had been performed.

Duration of disease: Pulmonary tuberculosis had been diagnosed prior to the age of fifty in 22 patients. In 9 of these, the ipsilateral lung had been treated with artificial pneumothorax; in 6, with thoracoplasty; in one, with extraperiosteal plombage; and in one, with phrenic crush and pneumoperitoneum. Three

additional patients had received sanatorium care. Two had had no previous treatment.

Tuberculosis was diagnosed in 14 patients after the age of fifty. In one of them the contralateral lung had been treated with extrapleural plombage. Mass roentgenography was the means of detecting the disease in 9 of these 14 patients.

Bacterial findings: At the beginning of the treatment period leading up to pulmonary resection, tubercle bacilli were found in the sputum on microscopy in 31 patients. Cultures of sputum or gastric aspirates showed tubercle bacilli in 4 of the remaining 5 cases. In the patient with negative tests, lobectomy was performed for bronchiectasis with repeated hemoptyses following a finding of sputum positive for *M. tuberculosis* nineteen years previously.

Bronchoscopic findings: In 24 patients bronchoscopy disclosed no abnormality. Tuberculous endobronchial lesions were observed in 12 patients. Irreversible stenosis was present in 3 of the patients submitted to pneumonectomy, in 3 treated with lobectomy, and in one with segmental resection.

State of the contralateral lung: When hospitalized in preparation for excisional surgery, 14 patients had tuberculous infiltration of the contralateral lung. This was judged to be active in 3 cases. No patient had contralateral cavitation.

Pulmonary function: In 29 of the 36 patients, spirometric analysis of lung function was carried out before resection. The results are presented in tables 3 and 4. In the former table, comparison is made with corresponding findings in various groups of healthy subjects. These values are cited from Greifenstein and associates (7). When allowance is made for the variations in mean age, the tuberculous patients compare favorably with the healthy persons. Particular importance was attached to the relationship of the residual volume to the total capacity and the maximal breathing capacity. In table 4 the observed maximal breathing capacity is compared with the predicted values for the same patients. This volume was calculated according to the formula of Baldwin and coworkers (8).

It must be remembered that, in many of these patients, long-standing tuberculous disease or its treatment had produced severe changes in the lung areas proposed for resection. This applied especially to the pneumonectomy cases, in which the indications for operation generally were such extensive unilateral lesions that the lung was practically functionless. Consequently it is not surprising that the poorest values were recorded in these patients.

In cases in which the spirometric readings made the advisability of operation doubtful, more detailed investigations were performed. These included cardiac catheterization with or without occlusion of the pulmonary artery. Electrocardiographic examination was made in all cases.

Antimicrobial therapy: All patients received antimicrobial drugs in the immediate preoperative and postoperative periods. Para-aminosalicylic acid (PAS) (10 gm. daily) and streptomycin or dihydrostreptomycin (1 gm. daily or thrice weekly) were given before operation in all cases. Most patients also received isoniazid (as a rule 6 mg. per kg. of body weight daily). Twenty-five patients had had previous treatment with antimicrobial drugs. Streptomycin had been used sparingly in order to conserve its effectiveness for the resection operation

TABLE 3

MEAN LUNG VOLUMES IN TUBERCULOUS AND NORMAL MIDDLE-AGED AND ELDERLY PERSONS

	Number of Subjects	Mean Age	Functional Residual Capacity	Vital Capacity	Residual Volume	Total Capacity	Residual Volume / Total Capacity × 100
		years					
Tuberculous males (Present study)							
Before lobectomy and/or segmental resection	16	53.4	3.43 (0.15)	4.36 (0.24)	2.08 (0.12)	6.44 (0.27)	32.6 (1.7)
Before pneumonectomy	3	51.4	2.63 (0.62)	2.94 (0.41)	1.64 (0.26)	4.58 (0.58)	35.6 (3.7)
Normal males (Author)							
Greifenstein *et al.*	11	61.5	3.44 (0.74)	3.48 (0.48)	2.43 (0.50)	5.92 (0.57)	40.9 (7.1)
Kraltreider *et al.*	18	57.9	2.17	3.85	1.50	5.35	28.0
Robinson	20	59.8	2.49	3.97	1.79	5.92	30.2
Gilson	10	54.3	3.90 (0.68)	4.26 (0.94)	2.50 (0.61)	6.80 (1.19)	37.4 (7.3)
Tuberculous females (Present study)							
Before lobectomy and/or segmental resection	6	55.4	2.15 (0.23)	2.87 (0.20)	1.33 (0.14)	4.20 (0.27)	31.5 (2.5)
Before pneumonectomy	4	58.4	1.95 (0.39)	2.14 (0.34)	1.38 (0.27)	3.52 (0.58)	38.8 (2.8)
Normal females (Author)							
Greifenstein *et al.*	14	60.9	2.22 (0.53)	2.34 (0.45)	1.78 (0.40)	4.14 (0.68)	41.9 (6.8)

The figures in parentheses represent standard deviations.

Surgical indications and technique: The indications for pulmonary resection in these patients did not differ from those employed in younger persons. Thus pneumonectomy was performed for pulmonary cavitation with severe bronchostenosis and for destroyed lung. Pleuropneumonectomy was carried out in cases of failed thoracoplasty or bronchopleural fistula with empyema (table 5). The indications for the other procedures were pulmonary cavitation with or without bronchostenosis, localized tuberculous bronchiectasis, or tuberculoma. A technically good pneumothorax which, however, failed to control the disease was abandoned in favor of excisional surgery in 2 cases.

Pulmonary resection and thoracoplasty were carried out as a single-stage procedure in 10 patients. In 7 of them the osteoplastic technique evolved by Björk (9) was used. Thoracoplasty was performed as the first stage of a multi-stage procedure in 12 cases and as the final stage in 3 (all pneumonectomies). In 5 segmental resections, one combined with lobectomy, thoracoplasty was con-

TABLE 4

OBSERVED AND PREDICTED MAXIMUM BREATHING CAPACITY IN PATIENTS MORE THAN FIFTY YEARS OF AGE

(Mean Values)

	Number of Patients	Mean Age	Observed Values	Predicted Values
Males				
Before lobectomy and/or segmental resection	16	53.4	96.6	112.4
			(5.6)	(2.2)
Before pneumonectomy	3	51.4	71.7	117.3
			(8.2)	(5.4)
Females				
Before lobectomy and/or segmental resection	6	55.4	69.6	80.0
			(1.8)	(2.2)
Before pneumonectomy	4	58.4	48.3	72.3
			(5.3)	(2.0)

The figures in parentheses represent standard deviations.

TABLE 5

INDICATIONS FOR PULMONARY RESECTION IN PATIENTS MORE THAN FIFTY YEARS OF AGE

Indication	Pneumonectomy	Lobectomy	Lobectomy Plus Segmental Resection	Segmental Resection	Total
Pulmonary cavitation		6	4	6	16
Cavitation plus bronchostenosis	2	3		1	6
Tuberculous bronchiectasis		2	1		3
Empyema (bronchopleural fistula)	2*				2
Tuberculoma		1		1	2
"Destroyed lung"	1				1
Failed thoracoplasty	2*	3			5
Failed thoracoplasty plus bronchostenosis	1*				1
Total	8	15	5	8	36

* Pleuropneumonectomy.

sidered unnecessary. In the remaining 6 cases, resection was undertaken after thoracoplasty had failed. The resection operations were performed with Crafoord's technique, using spiropulsator respiration and Carlens' double-lumen bronchial catheter.

Results from Surgery

Of the 35 patients with tubercle bacilli in the sputum or gastric washings at the beginning of treatment, 17 still had positive tests at the time of operation. In all cases, however, the quantity of expectoration had diminished and the general condition had improved. No patient had active contralateral lesions when resection was performed.

Surgical mortality and complications: There were no surgical fatalities. Cardiac

arrest occurred during induction of anesthesia for a segmental resection, but the patient responded so well to treatment that the operation was continued. This patient already had extrapleural plombage of the contralateral lung. One week after segmental resection he developed acute respiratory distress which necessitated emergency tracheotomy. A roentgenogram then revealed spontaneous ipsilateral pneumothorax.

Following pneumonectomy 2 patients showed signs of incipient pulmonary edema. One of them had been considered a doubtful surgical risk because of preoperative pulmonary hypertension. In another patient intrapleural bleeding occurred postoperatively, presumably from an intercostal vessel, but did not require thoracotomy. Ipsilateral atelectasis necessitated bronchoscopic suction in 2 patients but was relieved with physiotherapeutic measures in a third. In a patient with lobectomy and a simultaneously performed small apical thoracoplasty, persistence of air in the operation field indicated bronchopleural fistula. Six months after operation, however, the air was completely reabsorbed. Reactivation of contralateral lesions which had become quiescent under preoperative antimicrobial therapy occurred in one patient. Satisfactory regress subsequently took place. Other complications were thrombosis of a crural vein and subcutaneous emphysema which required Bülau drainage. A survey of the surgical complications is presented in table 6.

Late complications and late mortality: Two months after pneumonectomy, a 62-year-old woman developed an ipsilateral pleural effusion which contained tubercle bacilli. Plombage of the space had been planned but, because of the effusion, a two-stage thoracoplasty was performed instead. This patient is still hospitalized five and one-half months after pneumonectomy and two months after thoracoplasty.

A 56-year-old man with a long history of mixed-infection empyema and pleurocutaneous fistulas was operated on for tuberculous osteochondritis one year before pleuropneumonectomy. Shortly after the latter intervention, the fistulas reopened in association with an attack of infectious hepatitis. Revision of the

TABLE 6

COMPLICATIONS OF PULMONARY RESECTION IN PATIENTS MORE THAN FIFTY YEARS OF AGE

Complication	Pneumonectomy	Lobectomy	Lobectomy Plus Segmental Resection	Segmental Resection	Total
Cardiac arrest during anesthesia induction				1	1
Incipient pulmonary edema	2				2
Intrathoracic bleeding	1				1
Ipsilateral atelectasis		2	1		3
Crural thrombosis		1			1
Contralateral progression			1		1
Bronchopleural fistula		1			1
Severe subcutaneous emphysema				1	1
Total	3	4	2	2	11

thoracoplasty was performed, and fifteen months later only an insignificant amount of serous fluid is being discharged onto the skin.

A 51-year-old man was discharged in satisfactory condition five months after extirpation of the right upper lobe and thoracoplasty. Two months later he died. No tuberculous lesions were demonstrable at autopsy. The cause of death was established as bronchopneumonia and nephrosclerosis.

Follow-up observations: At the end of the observation period (March 31, 1955) 35 patients were still alive. They had been followed for periods ranging from three months to five and one-half years after pulmonary resection.

Status of infectiousness: The sputum is now negative for tubercle bacilli on microscopy in all patients. Gastric aspirates have been examined postoperatively in 11 patients, and guinea pig tests and cultures of these specimens were negative for tubercle bacilli. Sputum cultures were also "negative" in 6 of the 8 patients so examined. Of the 2 patients with infectious sputum, one is a 52-year-old woman who developed carcinoma of the stomach nine months after lobectomy with segmental resection. The other is a 54-year-old man in whom the apicoposterior segment of the right upper lobe and the apical segment of the right lower lobe were excised in 1952. A more extensive intervention was indicated but was precluded by relatively poor pulmonary function. In the former patient there is no roentgenographic evidence of active tuberculosis. Contralateral lesions are suspected to be active in the latter patient. In all the others the postoperative roentgenograms are satisfactory.

Working capacity: A survey of the patients' present working capacity is given in table 7. Twenty patients have been classed as fit for full-time or part-time work. These include housewives who have resumed their usual or lighter duties.

TABLE 7

ECONOMIC RESULTS OF PULMONARY RESECTION IN PATIENTS MORE THAN FIFTY YEARS OF AGE

Observation Period	Fit for Work			Unfit for Work				Dead of Non-tuberculous Disease	Total
	Working		No Suitable Work Available	Convalescent After Pulmonary Resection	Active Tuberculosis	Other Causes			
						Bacillary Findings			
	Full Time	Part Time				Positive	Negative		
6 months				5					5
6 months–1 year	2	2	1	3					8
1–2 years	5	3	1	2		1		1	13
2–3 years	2	1			1				4
3–4 years	1						3		4
4–5 years	1								1
5–6 years	1								1
Total	12	6	2	10	1	1	3	1	36

Ten patients are regarded as convalescent after pulmonary resection. Two are still convalescent after more than a year; they were in relatively poor condition before the operation, due respectively to gastric ulcer with severe hematemeses and failed thoracoplasty. Three patients are unfit for work despite stable pulmonary roentgenograms and sputum cultures or gastric washings negative for tubercle bacilli. One is receiving psychiatric care, one has angina pectoris, and the third is prevented from working by pain in the ipsilateral arm and shoulder, for which there is no demonstrable objective cause.

Cosmetic results: The cosmetic results were good in this series. Although all 6 patients with failed thoracoplasty presented some degree of spinal deformity before pulmonary resection (slight in one, moderate in 2, and severe in 3), this was in no case made worse by the later operation. Of the other 30 patients, 4 now have mild scoliosis; in 2 cases following pneumonectomy with ten-rib thoracoplasty, in one with lobectomy and removal of the second to the sixth ribs, and in another with lobectomy and osteoplastic thoracoplasty by the Björk technique. Much of the credit for these good results must be attributed to the care with which physiotherapeutic instruction and treatment were given before and after operation.

DISCUSSION

In discussing the indications for collapse therapy and pulmonary resection, Bruce (10) concluded very recently that resection should have clear precedence in bronchial tuberculosis, bronchopleural fistula, tuberculoma, tuberculous bronchiectasis, persistent cavitation after artificial pneumothorax or thoracoplasty, and cavitary tuberculosis in which the outlook for collapse therapy is unfavorable. The last-named indication is frequently presented by the fibrous cavity walls in older tuberculous patients.

Because diabetes and tuberculosis may influence each other so markedly, extirpation of a pulmonary tuberculous focus is the procedure most likely to give rapid control of both diseases when they coexist. Four patients in the present series had diabetes. In all of them the results of operation were good.

In elderly and middle-aged candidates for pulmonary resection, tests of cardiorespiratory function must be more frequently employed and perhaps be more elaborate than in younger patients. In the present study, evaluation of function was made according to the principles described by Björkman and associates (11). Thus, in spirometry, the main emphasis was placed on the maximal breathing capacity and the relationship of the residual volume to the total capacity. Bronchospirometry and cardiac catheterization, with or without occlusion of the pulmonary artery, were performed in doubtful cases. Even in older patients however, detailed function tests may not be required if standard clinical tests give favorable results. The extirpation of a destroyed segment, lobe, or lung will not necessarily reduce respiratory efficiency. On the contrary, an improvement may result from the elimination of a shunt mechanism frequently present in the pulmonary ventilation.

Avoidance of spinal deformities with their deleterious effects on cardiorespiratory function is particularly important in older patients. In this series the only severe deformities seen were the result of previous thoracoplasty.

By bed rest and drug therapy it was attempted to satisfy the other criteria of operability, viz., conversion to inactivity of any pulmonary lesions outside the area to be excised, minimal sputum, and negative bacteriologic tests. It was not surprising, however, that in 17 patients the sputum or gastric aspirates still showed tubercle bacilli at the time of resection. Several of these patients had severe bronchostenosis and many had old, thick-walled cavities.

One of the reasons for the widespread popularity of pulmonary resection is the considerable decline which has taken place in its mortality rate. In more than 100 patients of all ages from Söderby Hospital who underwent pulmonary resection from March, 1954, to March, 1955, only one surgical fatality occurred (10). In an earlier series of patients from similar sources, Johansson and Uggla (12) reported that 6 of 19 patients operated on between 1935 and 1948 died in the immediate postoperative period. Only one postoperative death occurred in the 35 patients who underwent excisional surgery from 1948 to 1950. Mortality figures are scarce for the older age groups. In the study of Davidson and associates (4), the "over-all death rate" in patients aged fifty years or more and subjected to pulmonary resection between 1944 and 1952 was 33.3 per cent. The death rates in all age groups were found roughly to parallel the increasing age decades. In the light of this finding the absence of surgical deaths in the present series is highly encouraging.

The low frequency of bronchopleural fistula in the present study (one patient) also bears witness to the high standard of modern surgical technique.

Although the observation period is short in many cases, it is gratifying that no less than 20 of the patients are fit for full-time or part-time work. If one excepts the 8 patients regarded as convalescent less than a year after pulmonary resection, 71 per cent of the series are now fit for some type of work. The fact that in 2 cases no suitable employment is available, however, illustrates the difficulties which beset the rehabilitation of some older tuberculous patients, particularly those formerly engaged in heavy manual work.

It is too early to attempt a long-term prognosis in regard to cardiorespiratory function. Postoperative function measurements are not yet available for most of the patients. Nevertheless, the study shows that patients with values of the order found in the present study are well able to tolerate pulmonary resection.

In earlier papers (5, 6) the therapeutic possibilities of artificial pneumothorax and thoracoplasty in older tuberculous patients were discussed. The opinion was expressed that, provided a careful watch is kept for complications which may damage respiratory function, pneumothorax still warrants trial in carefully selected cases. The indications for thoracoplasty have been considerably limited by the progress made in excisional surgery. Thoracoplasty, however, is well suited for some types of tuberculosis in older patients. The results in the present study indicate that pulmonary resection offers encouraging possibilities of rehabilitating many middle-aged and elderly tuberculous patients who otherwise

would have to suffer the social consequences of infectiousness in addition to the constant risk of progression.

SUMMARY

A report is presented of 36 pulmonary resections performed during the period from November, 1949, to December, 1954, in patients more than fifty years of age.

In every case but one, tubercle bacilli were found in the sputum or gastric washings. The indications for pulmonary resection were cavitary disease of the lung with or without bronchostenosis, thoracoplasty failure, tuberculous bronchiectasis, empyema with bronchopleural fistula, tuberculoma, and destroyed lung.

Spirometric studies of pulmonary function were performed before operation in 29 cases. All of the patients received antimicrobial drugs before and after surgery.

Pleuropneumonectomy was performed in 5 cases, pneumonectomy in 3, lobectomy in 15, lobectomy with segmental resection in 5, and segmental resection alone in 8 cases.

There were no surgical fatalities and no patient has died postoperatively as the result of the tuberculous disease. The main surgical complications were cardiac arrest during induction of anesthesia (one case), incipient pulmonary edema (2 cases), and atelectasis (3 cases). Bronchopleural fistula occurred in one patient but healed within six months. A pleurocutaneous fistula reopened after pleuropneumonectomy for prolonged empyema.

The patients were followed for periods ranging from three months to five and one-half years. At the end of the observation period (March 31, 1955) 20 patients were fit for full-time or part-time work and 10 were still regarded as convalescent after pulmonary resection. Four were classified as unfit for work for reasons other than tuberculosis. In all but one of them (a patient with carcinoma of the stomach), sputum cultures or gastric washings were negative for tubercle bacilli. One patient was ill with tuberculosis and one had died of nontuberculous disease.

In older, as in younger, tuberculous patients, excisional surgery is gaining ground at the expense of collapse therapy. The present study shows that pulmonary resection is well tolerated by persons older than fifty years. With careful treatment and observation before and after operation, particularly in regard to conservation of respiratory function, age as such should not be accepted as a contraindication to pulmonary resection.

SUMARIO

La Resección Pulmonar en los Enfermos de Edad Mediana y Avanzada

Preséntase una reseña de 36 resecciones pulmonares ejecutadas durante el período de noviembre, 1949, a diciembre, 1954, en sujetos de más de cincuenta años de edad.

En todos los casos, menos uno, descubriéronse bacilos tuberculosos en el esputo o los lavados gástricos. Las indicaciones de la resección pulmonar fueron: afección cavitaria del pulmón con o sin broncostenosis, fracaso de la toracoplastia, bronquiectasia tuberculosa, empiema con fístula broncopleural, tuberculoma y destrucción del pulmón.

En 29 casos, hiciéronse estudios espirométricos de la función pulmonar antes de la operación. Todos los enfermos recibieron drogas antimicrobianas antes y después de la cirugía.

Se ejecutó la pleuroneumonectomía en 5 casos, la neumonectomía en 3, la lobectomía en 15, la lobectomía con resección segmental en 5 y la resección segmental sola en 8.

No hubo mortalidad quirúrgica y ningún enfermo ha fallecido postoperatoriamente a consecuencia de la enfermedad tuberculosa. Las principales complicaciones quirúrgicas fueron: paro del corazón durante la inducción de la anestesia (un caso), edema pulmonar incipiente (2 casos) y atelectasia (3 casos). Hubo fístula broncopleural en un sujeto, pero cicatrizó en término de seis meses. Una fístula pleurocutánea volvió a abrirse después de una pleuroneumonectomía por empiema prolongado.

Los enfermos fueron mantenidos en observación durante períodos que variaron de tres meses a cinco años y medio. Al final del período de observación (31 de marzo de 1955), 20 enfermos se hallaban total o parcialmente capacitados para el trabajo y a 10 se les consideraba todavía como convalecientes después de la resección pulmonar. A 4 se les clasificó como inéptos para el trabajo por razones distintas de la tuberculosis. En todos, menos uno de ellos (sujeto con carcinoma gástrico), los cultivos del esputo o los lavados gástricos resultaron negativos para bacilos tuberculosos. Un sujeto estaba enfermo con tuberculosis y otro había fallecido de afección no tuberculosa.

En los tuberculosos de edad más avanzada, lo mismo que en los más jóvenes, la cirugía excisional va ganando terreno a costas de la colapsoterapia. El estudio actual demuestra que la resección pulmonar es bien tolerada por personas de más de cincuenta años de edad. Con el cuidadoso tratamiento y observación antes y después de la operación, en particular con respecto a la conservación de la función respiratoria, no debe aceptarse la edad por sí sola como contraindicación de la resección pulmonar.

RESUME

Résection pulmonaire chez le malade d'âge moyen et le vieillard

Présentation d'un rapport concernant 36 résections pulmonaires pratiquées pendant la période novembre 1949-décembre 1954 chez des malades âgés de plus de 50 ans.

Dans tous les cas sauf un, le bacille tuberculeux a été découvert dans les crachats ou les spécimens de lavage gastrique. Les indications de l'exérèse pulmonaire consistaient en: cavernes pulmonaires avec ou sans bronchosténose, échecs de la thoracoplastie, bronchiectasie tuberculeuse, empyème avec fistules broncho-pleurales, tuberculome et destruction du poumon. Les études spirométriques de la fonction pulmonaire ont été effectuées dans 29 cas avant l'intervention. Tous les malades recevaient la médication antibiotique avant et après l'intervention.

La pleuropneumonectomie a été effectuée dans 5 cas, la pneumonectomie dans 3 cas, la lobectomie dans 15 cas, la lobectomie avec résection segmentaire dans 5 cas et la segmentectomie seule dans 8 cas.

Il ne s'est produit aucun décès dû à l'intervention et aucun décès post-opératoire imputable à la tuberculose. Les principales complications d'ordre chirurgical ont été l'arrêt du coeur au cours de l'anesthésie (un cas), l'oedème pulmonaire au stade initial (deux cas) et l'atélectasie (trois cas). Chez un malade il s'est produit une fistule broncho-pleurale qui s'est rouverte après une pleuro-pneumonectomie pour empyème prolongé.

Les malades sont restés en observation pendant des périodes allant de 3 mois à 5 ans et demi. A la fin de la période d'observation (31 mars 1955), 20 malades étaient en état d'effectuer un travail à temps complet ou à temps partiel et 10 étaient encore considérés comme des convalescents après résection pulmonaire. Quatre malades ont été considérés incapables de travailler pour d'autres raisons que la présence de tuberculose. Chez tous, sauf un, (malade atteint de cancer de l'estomac), les cultures de crachat ou les lavages gastriques se sont avérées négatives pour la recherche du B.K. Un malade a présenté une tuberculose en activité et un autre est mort d'une infection non tuberculeuse.

Chez les tuberculeux pulmonaires, jeunes ou âgés, la chirurgie d'exérèse gagne du terrain aux dépens de la collapsothérapie. L'étude actuelle indique que la résection pulmonaire est bien tolérée après cinquante ans. Un traitement prudent et la surveillance du patient avant

et après l'intervention, en particulier à l'égard de la préservation de la fonction respiratoire, rend le facteur âge négligeable comme contre-indication de l'exérèse pulmonaire.

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ULTIMATE OUTCOME OF PATIENTS WITH VOCAL-CORD PARALYSIS OF UNDETERMINED CAUSE[1,2]

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This paper is primarily a report of a follow-up study of patients with vocal-cord paralysis of undetermined cause. The study was undertaken to answer two questions: (*1*) How many patients are living five years after diagnosis of such paralysis? (*2*) How many patients have voice complaints five years later?

The causes and the classification of vocal-cord paralysis have been discussed extensively in the literature (1–5). The relationship of such paralysis to thyroid operations (6, 7), cancer (8), heart disease (9), and vascular lesions is known. Methods of surgical treatment of vocal-cord paralysis (3, 10–14) have been greatly improved in the past two decades, and new anatomic concepts of the recurrent laryngeal nerve (7, 15) have been helpful to the laryngologist and to the surgeon in understanding the nature of the condition. Nevertheless, vocal-cord paralysis of undetermined cause has not been studied adequately from a prognostic standpoint, so far as the present writers know; hence, the present study has been made.

MATERIAL

In the ten-year period, 1940 to 1949 inclusive, 633 patients with vocal-cord paralysis were seen at the Mayo Clinic. In the present study the records of these patients were reviewed and the patients were classified according to the cause of the paralysis (table 1). Among the 633 patients were 181 with vocal-cord paralysis of undetermined cause; the records of these were studied in detail, and follow-up information was obtained by re-examination of the patients or by correspondence with the patients or with their physicians if the patients were deceased.

RESULTS

Clinical and Laboratory Data

The 181 patients with vocal-cord paralysis of undetermined cause represent 28.6 per cent of the entire series. There were 124 males and 57 females (a ratio of more than 2 to 1), and the left cord was paralyzed approximately twice as often as the right (113 to 59). The average age was fifty years.

The 181 patients were placed in five categories on the basis of common factors associated with the onset of symptoms (table 2). The 5 patients who had had cancer were included because an interval of five years or more had elapsed since they had been treated and there was no evidence of cancer; it was assumed that

[1] From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of The Graduate School of the University of Minnesota.

[2] Presented before the Medical Session, as part of *Section 4A*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 24, 1955.

TABLE 1

VOCAL-CORD PARALYSIS: CLASSIFICATION ACCORDING TO CAUSE OF PARALYSIS

Cause	Patients	Per Cent
Post-thyroidectomy	273	43.1
Cancer	95	15.0
Cardiovascular disease	26	4.1
Neurologic disease	22	3.5
Surgery (other than thyroid and cancer)	14	2.2
Trauma	13	2.1
Infection	9	1.4
Undetermined	181	28.6
Total	633	100.0

TABLE 2

VOCAL-CORD PARALYSIS: CATEGORIES OF PATIENTS BASED ON COMMON FACTORS ASSOCIATED WITH THE ONSET OF SYMPTOMS

Common Factor		Cases
Respiratory infection preceded symptoms		31
Upper respiratory infection	28	
Pneumonia	1	
Bronchiectasis	1	
Acute febrile illness	1	
Mechanical factors preceded symptoms		6
After clearing throat	2	
After coughing	2	
After shouting or prolonged talking	2	
"Benign masses," without previous surgical treatment		29
Adenomatous goiter	18	
Substernal goiter	10	
Pharyngo-esophageal diverticulum	1	
Cancer (prior to vocal-cord paralysis)		5
Left parotid tumor (15 years)	1	
Carcinoma of cervix (5 years)	1	
Cancer of breast (7 years)	1	
Cancer of breast (14 years)	1	
Multiple myeloma (10 years)	1	
None		110
Total		181

the vocal-cord paralysis represented a different disease process. As will be shown later, the truth of this assumption has been borne out.

Hoarseness or other voice symptoms, such as a weak voice, change in voice volume, pitch, or tones, loss of voice, and inability to sing, were the most frequent. Other frequently occurring symptoms or signs were dysphagia, dyspnea, cough, pain in the chest or throat, goiter, loss of weight, production of sputum,

TABLE 3

VOCAL CORD PARALYSIS: SYMPTOMS AND SIGNS IN 181 CASES

Symptom or Sign	Number	Per Cent of 181 Cases
Hoarseness	135	74.6
Other voice changes	28	15.5
Dysphagia	25	13.8
Dyspnea	18	9.9
Cough	17	9.4
Pain (chest 6, throat 7, neck 1)	14	7.7
Goiter	11	6.1
Neurologic (anisocoria 1, deviation of tongue 2, ptosis 1, numbness 2, facial tic 1)	7	3.9
Loss of weight	7	3.9
Sputum	6	3.3
Phlegm or "something" in the throat	6	3.3
Recurrent fever	3	1.7
Arthritis	3	1.7
Regurgitation	2	1.1
Nervousness	1	0.6
Plugged ear	1	0.6
Indigestion	1	0.6
Sore mouth	1	0.6
Laryngeal tumor	1	0.6

phlegm or "something in the throat," and various neurologic manifestations (table 3).

All but 8 of the 181 patients had general physical and laboratory examinations. Six patients who underwent lateral roentgenographic examination of the thorax were found to have no abnormality.

One hundred and seventy-three patients were examined roentgenographically and 43 of these were found to have some abnormality on the postero-anterior film of the thorax (table 4). Of the remaining 130 patients, 9 had minimal calcification or fibrosis in one or both apices which was interpreted by the radiologist as being due to ancient arrested tuberculosis. The roentgenograms of these 9 patients were placed in the negative group in the analysis.

Some of the "abnormalities" listed were very minor and would frequently be interpreted as being within normal limits. However, to be completely inclusive and to present the data without bias or selection, all abnormalities are included except the 9 instances of minimal calcification or fibrosis mentioned in the preceding paragraph. The inclusion of minor abnormalities is an important point because, as will be shown in the survival data, abnormal findings on roentgenographic examination of the thorax have prognostic significance.

Esophagograms were interpreted as normal in 29 of 36 cases. One hiatal hernia, two substernal goiters, one pharyngo-esophageal diverticulum, one duodenal ulcer, one esophageal stricture, and one case of scleroderma of the esophagus were noted.

TABLE 4

VOCAL-CORD PARALYSIS: ROENTGENOGRAPHIC DATA

Diagnosis	Cases	
Mediastinum		14
Substernal goiter	10	
Mediastinal node (?)	1	
Tumor, right superior mediastinum	1	
Tumor, left superior mediastinum	1	
Widening of mediastinum	1	
Hilus		11
Increased left hilar marking	4	
Calcified hilar nodes	4	
Hilar vascular congestion	2	
Retraction, both hilums	1	
Heart		6
Cardiac enlargement	4	
Prominent left ventricle	2	
Parenchyma of lung		6
Emphysema	3	
Atelectasis, left lower lobe	1	
Tumor, left lung	1	
Pulmonary fibrosis	1	
Inflammation		5
Bronchiectasis	2	
"Can't exclude tuberculosis"	2	
Inflammatory process	1	
Ribs		1
Density in sixth rib posteriorly	1	
Total		43

Roentgenograms of the skull were interpreted as normal in 15 of 20 patients. Hyperostosis was noted twice; osteoporosis, once; surgical bone defect and a questionable erosion of the sella, once; and calcification of the falx, once.

Fluoroscopic examination of the thorax gave normal results in 10 of 19 patients. Substernal goiter was observed three times; torsion of the aorta, four times; diaphragmatic tic, once; and limited excursion of the diaphragm, once.

Bronchoscopic examination gave normal results in 6 of 9 patients. One patient had compression of the trachea and 2 had inflammatory conditions according to biopsy reports. None of the 181 patients underwent bronchographic examination.

Esophagoscopic examination gave negative results in 3 of 4 patients; an inflammatory stricture, following roentgen therapy for carcinoma of the breast, was noted in the other patient.

The sputum from 21 patients was examined. Examination for tubercle bacilli gave negative results twenty-two times in 16 patients, and examination for malignant cells gave negative results ten times in 5 patients. Tomograms of the larynx made in 2 cases disclosed no abnormality in one case and minimal laryngeal thickening in the other.

TABLE 5

VOCAL-CORD PARALYSIS: FIVE-YEAR AND TEN-YEAR SURVIVAL RATES ACCORDING TO ROENTGENOGRAPHIC FINDINGS ON THORACIC EXAMINATION

Roentgenographic Findings	Patients		Lived Five or More Years After Diagnosis at Clinic		Patients		Lived Ten or More Years After Diagnosis at Clinic	
	Total	Traced	Number	Per Cent*	Total	Traced	Number	Per Cent*
Negative	138	135	129	95.6	57	53	44	83.0
Positive	43	41	24	58.5	26	24	13	54.2
Total	181	176	153	86.9	83	77	57	74.0

* Based on traced patients. Inquiry as of January 1, 1955.

Survival Data

Follow-up information was obtained on 176 (97.2 per cent) of the 181 patients. Of these 176 patients, 135 were living and 41 were dead.

The five- and ten-year survival rates for the group of 181 patients with vocal-cord paralysis were 86.9 per cent and 74.0 per cent, respectively (table 5). The estimated corresponding rates for a "normal" population of similar age and sex distribution are 95 per cent and 87 per cent, respectively (16, 17). Thus, for the group of patients with vocal-cord paralysis of undetermined cause, the five-year and ten-year survival rates were somewhat below those for a "normal" population.

A breakdown of the group into patients with and patients without positive findings on roentgenographic examination of the thorax (table 5) shows that those with negative roentgenographic findings may be expected to live a "normal" life. The five- and ten-year survival rates were 95.6 per cent and 83.0 per cent, respectively. The outlook for those exhibiting any positive roentgenographic finding is not so favorable, the five- and ten-year survival rates for these being 58.5 per cent and 54.2 per cent, respectively.

Because of inadequate numbers of cases, survival rates were not calculated with respect to other findings. However, it should be noted that 6 of 7 patients who complained of loss of weight are dead, 7 of 17 patients who complained of cough are dead, and 5 of 14 patients who complained of pain are dead.

The exact cause of death is unknown in 20 of the 41 patients who died. Of the 21 deaths for which the cause is known, 11 were due to neoplasm: cancer of the bronchus caused six deaths; cancer of the larynx, two deaths; cancer of the thyroid, one death; and brain tumor and mediastinal tumor, one death each. Cardiovascular disease, including cerebrovascular accidents, caused eight deaths. One death was caused by bronchiectasis, and one death followed prostatectomy.

Of the 29 patients with benign masses in the neck, 22 are living, 5 have died, and 2 are untraced. Two patients with substernal goiters have died, one dying of an unknown type of carcinoma. One patient with a cervical goiter died of metastasis of bronchial carcinoma to the central nervous system, and the patient with a pharyngo-esophageal diverticulum died of a "much enlarged heart."

Of the 5 patients who had cancer prior to the diagnosis of vocal-cord paralysis, only one has died, and this death resulted from an undetermined cause six years after the diagnosis of vocal-cord paralysis, or twenty years after treatment of cancer of the breast. The results would seem to be justification for including in the undetermined group the 5 cases in which cancer apparently had been successfully treated at least five years prior to the diagnosis of vocal-cord paralysis.

Subsequent Diagnosis of the Etiologic Agent

A definite or presumptive cause for the vocal-cord paralysis has been determined in 5 of the 135 living patients. One patient was operated on for brain tumor eight years after the onset of vocal-cord paralysis, and another was operated on for cranial hemangioblastoma four months after the onset of such paralysis. One patient underwent radiation treatment of a chemodectoma of the glomus jugulare, the diagnosis being verified by means of a biopsy specimen from the middle ear, five years after the onset of vocal-cord paralysis (18). One patient had a pharyngo-esophageal diverticulum, which was diagnosed seven years after the onset of vocal-cord paralysis. In the remaining patient, cancer of the breast developed four years after the diagnosis of vocal-cord paralysis.

Adequacy of Examination

The cause of the vocal-cord paralysis was not discovered during life in the majority of the 41 patients who died. This finding naturally leads the physician to wonder just how thorough a clinical examination should be made in an attempt to discover the causative factor in such paralysis. It does not seem that hard and fast rules can be outlined. The diagnostic procedures performed must be individualized according to the symptoms of the patient and the judgment of the physician. The basic procedures should include a thorough history and physical examination, and in all cases a stereoscopic roentgenogram of the thorax should be made. If roentgenographic examination of the thorax disclosed abnormal shadows, then an intensive investigation is indicated, as illustrated in the following case.

A white man, 64 years of age, was seen on July 12, 1949, because of hoarseness which he had had for three months and which had followed "a touch of flu." He also complained of food lodging in his throat. A postero-anterior roentgenogram of the thorax showed hilar vascular congestion. A lateral roentgenogram of the esophagus as well as a roentgenogram of the head did not disclose any abnormality. The left vocal cord was paralyzed. On reexamination on November 29, 1949, a roentgenogram of the thorax did not present any evidence of disease. The left vocal cord was still paralyzed and no cause for the paralysis was found.

While leaving the city the patient had an automobile accident and was hospitalized because of a fractured sternum. He died of aspiration pneumonia. At necropsy a carcinoma of the left lower-lobe bronchus was found.

In retrospect, one wonders whether the diagnosis might have been established in this case if the sputum had been examined for malignant cells or if the patient had been examined bronchoscopically. Both of these procedures were done too few times in this series to permit statistical evaluation of their diagnostic ef-

fectiveness. It would seem that examination of the sputum and bronchoscopy are indicated in any case in which abnormal roentgenographic shadows are seen.

Status of the voice: It should be mentioned that the status of the voice is not a good criterion of vocal-cord paralysis. Such paralysis may be present in a patient who believes his voice to be normal, expecially if the paralysis has been present for some months or years and if the vocal cord in question has approached the midline and has come to rest in the position of phonation, so that the opposite cord can narrow the glottic chink in the usual manner during phonation.

The diagnosis of vocal-cord paralysis in all cases studied in this series was made by indirect laryngoscopy. Indirect laryngoscopy does not always establish the diagnosis easily and certainly. Even with paralysis of the recurrent nerve, there usually is some movement of the vocal cord, presumably by extrinsic muscles supplied by the superior laryngeal nerve. Sometimes abduction of the cord is limited in degree and it may be difficult to decide whether or not to consider the cord "paralyzed." Also there may be inhibitory fixation of a cord, as described by Havens (10); this is usually seen in the nervous, tense patient who may or may not be gagging, and repeated examinations may be necessary to get the patient to relax.

Occasionally there is marked rotation of the larynx due to a large unilateral adenoma of the thyroid gland. At times the vocal cord on the side of the adenoma may be restricted in its lateral movement and appear to be paralyzed.

In the majority of patients in this study, laryngeal examination to determine whether function of the vocal cord had returned was not made at the time of this study because of the impossibility of having the patients return.

Of the 107 living patients on whom reports on the status of the voice were obtained, only 35 had return of normal voice.

Dysphagia was present in 27 of the 107 patients (table 6). The difficulty in swallowing experienced by patients with unilateral vocal-cord paralysis usually consists of episodes of choking and coughing brought about by attacks of laryngeal spasm; this spasm is induced by food or liquids which enter the larynx, presumably on the side of paralysis. It occurs usually when the patient becomes careless while eating, and often he will say "I have to be careful when I eat."

Unilateral vocal-cord paralysis alone does not cause dyspnea. In the present

TABLE 6

VOCAL-CORD PARALYSIS: ASSOCIATED COMPLAINTS OF 107 LIVING PATIENTS ON WHOM REPORTS ON THE STATUS OF THE VOICE WERE OBTAINED

Complaint	Voice Normal (35 Patients)	Voice Abnormal (72 Patients)	Total
Dysphagia	4	16	20
Dyspnea	2	5	7
Dysphagia and dyspnea	0	7	7

series, 14 of 107 patients complained of dyspnea (table 6). This can mean one of two things: either that the unilateral paralysis had become bilateral or that there were other causes of the dyspnea.

Vocal-cord paralysis following a respiratory infection might be expected to disappear as a rule. In the present series, however, subjective return of the voice to normal was reported by only 7 of 31 such patients. Six of these 31 have died, no information regarding the voice of 6 living patients is available, and 12 patients still have abnormalities of the voice.

SUMMARY

In a study of 633 cases of vocal-cord paralysis, no cause for the paralysis could be found in 181 cases. Follow-up information was obtained on 176 of the 181 patients and five-year and ten-year survival rates were calculated.

On the basis of a statistical analysis of the data from this study, it is concluded that a patient who has a vocal-cord paralysis of undetermined cause, but who otherwise appears normal on general examination, may be told that he can expect to live out his normal life span and that the chance of regaining his voice is one in three. If the patient has both vocal-cord paralysis and any abnormal shadows in the roentgenogram of the thorax, his chance of living five years is approximately three in five, and his chance of living ten years is a little more than one in two.

SUMARIO

El Pronóstico de la Parálisis de las Cuerdas Vocales Debida a Causa Indeterminada

En un estudio de 633 casos de parálisis de las cuerdas vocales, no pudo descubrirse la causa en 181 casos. Obtúvose información subsecuente en 176 de los 181 enfermos y se calcularon los coeficientes de sobrevivencia de cinco y de diez años.

A base de un análisis estadístico de los datos arrojados por este estudio, dedúcese que, a un enfermo que tiene una parálisis de las cuerdas vocales de causa indeterminada, pero que en lo demás parece normal en el examen general, cabe decirle que puede esperar una vida de duración normal y que, de cada tres probabilidades de recobrar el uso de la voz, tiene en su favor una. Si tiene tanto parálisis de las cuerdas vocales como alguna sombra anómala en las radiografías del tórax, sus probabilidades de vivir cinco años son de tres en cinco y las de vivir diez años poco más de una en dos.

RESUME

Pronostic de la paralysie des cordes vocales de cause indéterminée

Dans une étude de 633 cas de paralysie des cordes vocales, la cause de la paralysie est restée inconnue dans 181 cas. Les renseignements obtenus en suivant 176 cas sur 181 ont permis d'établir des taux de survie de cinq et dix ans.

Sur la base d'une analyse statistique des données de l'étude, l'auteur conclut qu'un patient atteint de paralysie des cordes vocales de cause indéterminée, mais qui d'autre part apparaît normal à l'examen général, peut être informé qu'il peut s'attendre à une durée de vie normale et que ses chances de recouvrer sa voix sont de une sur trois. Si, en même temps que la paralysie des cordes vocales les radiogrammes montrent des opacités anormales, les chances du malade de vivre encore cinq ans sont approximativement de trois sur cinq, et ses chances de vivre dix ans de une sur deux.

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SELECTIVE ANGIOPNEUMOGRAPHY AND A CORRELATIVE STUDY OF BRONCHOGRAPHY AND THE HISTOPATHOLOGIC FINDINGS IN TUBERCULOUS FIBROTHORAX[1]

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INTRODUCTION

The roentgenographic study of pulmonary fibrosis, especially tuberculous fibrothorax, offers many interesting aspects which represent important anatomic and physiologic alterations. Several writers have studied the various roentgenographic patterns of fibrothorax. Steinberg and Robb (1), studying two non-tuberculous cases, concluded that the identification of vascular elements might be accomplished by angiocardiography in the oblique position; Fasano and Gasparri, using the same method, reported their findings in forty-eight tuberculous cases of fibrothorax and reached similar conclusions (2). Nevertheless the method used, namely the injection of contrast medium through the veins of an arm, does not give a satisfactory angiographic detail of the pulmonary vessels. The majority of the available publications do not contain studies which focus special attention on the fibrous pulmonary forms of tuberculosis.

Olson and associates (3), studying the pathology of the main bronchial alterations of pulmonary tuberculosis, found that only 60 per cent of the cases diagnosed by means of bronchography could be confirmed on microscopic examination. Blum and Quarz (4) point out that, by simple comparison of the angiopneumographic and bronchographic images of pulmonary tuberculosis, a strict correlation between both images does not exist. The pathology of the bronchi and the pulmonary vessels has been reviewed by numerous writers who agree for the most part and stress the fact that bronchiectasis is a frequent occurrence in forms of pulmonary tuberculosis with interstitial fibrosis (3, 5); bronchiectasis may be independent from the bronchial tuberculosis as such (6). The histologic changes of the arteries are of a hypertrophic and arteritic type, affecting mainly the intimal and muscular layers (5, 7–9) and are by no means specific for tuberculosis (9–13).

As demonstrated by Chávez, Dorbecker, and Celis (14) and by Jönsson, Brodén, and Karnell (15, 16), selective angiocardiography by direct intracardiac catheterization makes possible the anatomic diagnosis of the heart chambers and pulmonary vessels with the greatest accuracy. The selective angiopneumography used by Bolt and associates, and by Zörn and Worth in silicosis (17, 18) and by Bolt and Rink in tuberculosis (19, 20) discloses precise angiopneumographic details of the pulmonary vascular arrangement. The latter writers point

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out the possibility that some of the modifications observed by them could be caused by a process of obliterative angiitis. Earlier studies in which angiopneumography was used in tuberculosis have demonstrated that, in the fibrous forms, the circulation is notoriously diminished (21–23). On the other hand, in some cases of advanced pulmonary tuberculosis, as well as in nontuberculous bronchiectasis, it is possible to find important differences between the pre- and post-mortem angiographic studies obtained on the same person; these differences have not been completely explained (9).

The present work is concerned mainly with the study of some of the factors responsible for the profound anatomic and physiologic alterations which exist in tuberculous fibrothorax. An attempt has been made to relate the angiopneumographic, bronchographic, and pathologic findings.

MATERIALS AND METHODS

Thirty-six patients, 22 males and 14 females, whose ages ranged between thirteen and forty-eight years, were studied; of these, 33 patients had left and 3 had right-sided fibrothoraces. The choice of cases was fundamentally based on the findings of the postero-anterior chest roentgenogram. In all of the patients there was a hemithoracic opacity which fused itself with the cardiac shadow. Pronounced retraction of the mediastinal structures toward the affected side was present; usually an important costal retraction and a considerable elevation of the corresponding diaphragm were observed. In all cases the spine was clearly visible outside the mediastinal limit ("uncovered spine").

A detailed clinical study was performed on all of these patients, and all of them had tubercle bacilli in the sputum.

Routine functional respiratory tests (maximal breathing capacity, ventilatory reserve, and vital capacity) were made. Bronchospirometry with the Carlens' catheter was performed in correlation with the spirometric tests. It is important to add that only patients without oxygen consumption on the affected side were selected for the study.

Angiopneumography

A catheter was introduced through the external jugular vein and an angiopneumographic plate was taken; then the pulmonary artery on the affected side was catheterized and the selective angiopneumography performed. It was possible to catheterize the pulmonary artery on the side of fibrothorax in 32 cases. Diodrast[1] was the contrast medium used; 15 to 20 ml. were employed for the global angiopneumography and 8 to 12 ml. for the selective procedure.[2]

Bronchography

All patients were subjected to bronchographic study (performed after the angiopneumogram). The direct catheterization of the bronchi by the method used by Di Rienzo (24) was employed and the entire corresponding bronchial tree was opacified. Several roentgenograms were taken in different positions; 40 per cent Lipiodol[3] was the contrast medium. The method employed by Gudberg (25) is not considered to be a good diagnostic procedure for these cases.

[1] Employed as 70 per cent Nosylan.[3]

[2] By "global angiopneumography" is meant the procedure by which the contrast medium is sent to the minor circulation from a place anatomically more or less distant to the pulmonary arterial tree. By "selective angiopneumography" is meant the procedure by which either the pulmonary artery or smaller ramifications, lobar or segmental, were approached directly when a special area was to be opacified, in accordance with the terminology of Jönsson and associates and Bolt and associates (15, 17).

Pathologic Study

Nineteen of the patients were subjected to pneumonectomy, and the resected lungs were studied histologically. The principal attention was directed to the vascular and bronchial structures, mainly those showing pronounced changes in the angiograms and bronchograms.

OBSERVATIONS

Angiopneumography

The findings from the global angiopneumographies were the same as those described by several writers (26, 27), namely, deviation of the superior vena cava and heart toward the affected side, a frequently dilated main pulmonary artery and complete absence of arterial arborizations in the diseased lung. For this reason, the survey was fundamentally a comparison between global and selective angiopneumographic findings.

When selective angiopneumography was possible, that is, when the catheter was introduced directly into the pulmonary artery of the affected side, a detailed visualization of the arterial tree was feasible. In these circumstances the global angiograms did not offer any visualization at all. In 32 cases in which selective angiopneumography was performed, important alterations, some of which were well developed, were found. The most frequent picture was that of a "winter tree" with flexuous and distorted arterial branches, together with a diminution in number of the finer vessels (figures 1*A* and 5*A* and *B*). In some cases there was a small arterial stump without branches (figure 2*A*). Complete absence of the vascular tree also was observed (figure 3*A*).

Bronchography

A great variety of images was evidenced through the opacification of the bronchial tree on the side of fibrothorax. Some of the lungs showed practically no remnant lobar and segmentary arborizations; this was seen in those cases with the longest evolution (figures 3*B* and 4*B*). In other cases all of the lobar and segmental branches were identified (figures 2*B* and 4*A*), although they did show perfectly clear cylindrical and moniliform bronchiectasis. The bronchographic findings could be determinated by the fact that the predominant lesions in the lungs were either of the destructive or fibrotic type. The conventional roentgenogram of the chest gave no clue to the amount of pulmonary destruction and bronchial alterations.

Histopathologic findings

The histologic study of the resected lungs from a total of 19 cases was performed with special attention to the arteries and bronchi.

Most of the specimens were similar macroscopically, they were considerably thickened, and on section the parenchyma appeared of fibrous consistency; all of them were considerably diminished in size. The bronchi revealed ectasis of diverse types. Several of the lungs contained irregular cavities drained through bronchi of ectatic configuration. In only 3 cases were some lobar bronchial

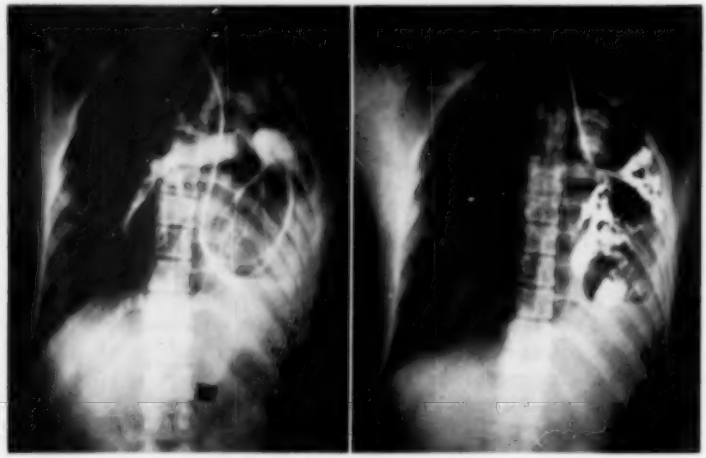

FIG. 1. E. V., a 40-year-old male patient. *A*. Selective angiopneumogram. The pulmonary artery on the left side is diminished in its caliber and shows only two branches with few arborizations. *B*. This patient had saccular and cylindric bronchiectasis and two large cavities filled with Lipiodol.®

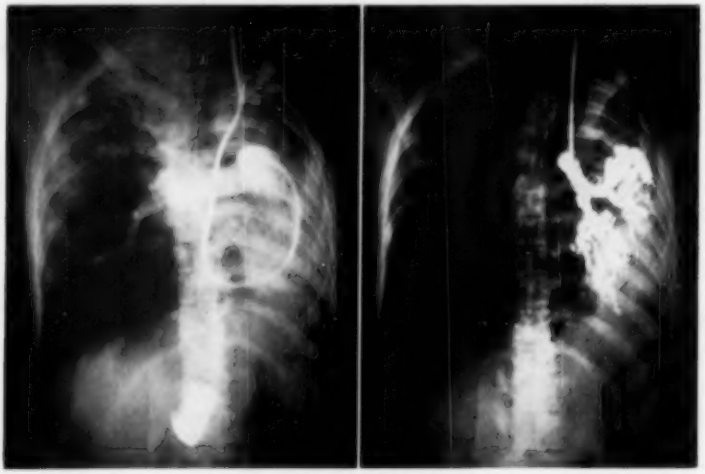

FIG. 2. A. G., a 20-year-old male patient. *A*. Selective angiopneumogram. There is only a small arterial stump on the left side. *B*. Cylindrical bronchiectasis of the lower lobe and lingula. There are several irregular cavities in the upper lobe.

branches found stenosed. In other cases, the lungs were virtually blocks of massive fibrosis in which the bronchial and arterial arborizations were almost totally absent.

In the pulmonary hilum the arterial vessels were considerably diminished in

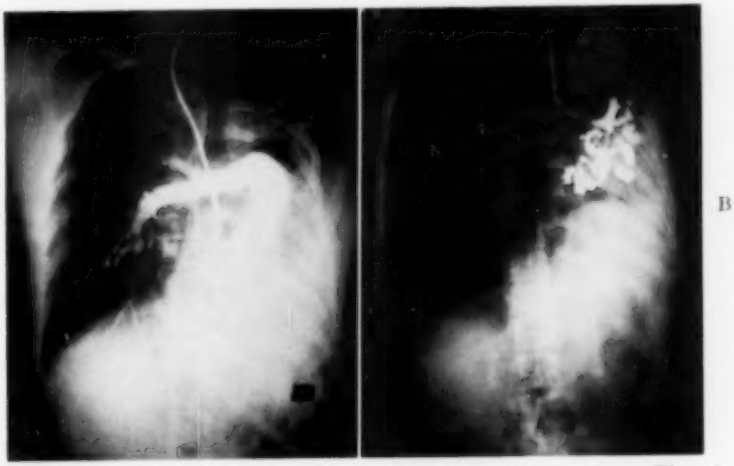

FIG. 3. L. L. A 23-year-old male patient. *A*. Selective angiopneumogram. There is no arterial tree on the left side. The histopathologic study showed obliteration of the main artery. *B*. There are several irregular cavities in the bronchogram.

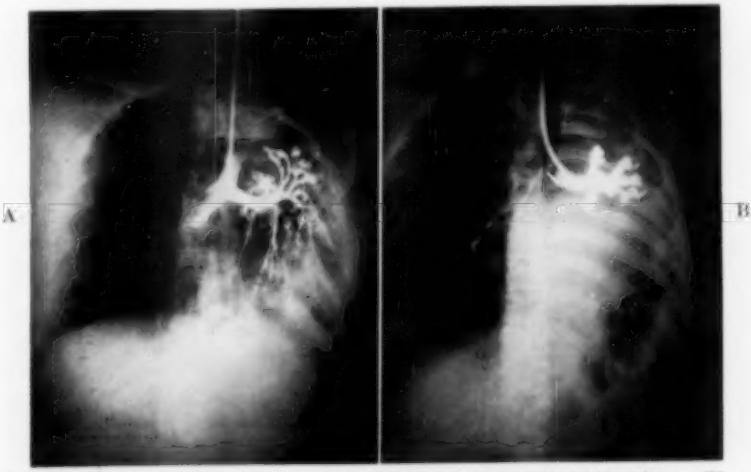

FIG. 4. *A*. S. O., a 48-year-old female patient. Pleurogenous type of fibrothorax. There is cylindric bronchiectasis in the upper lobe. The lower lobe bronchi are found to be straight and with few branches. *B*. A. C., a 26-year-old male patient. Massive pulmonary fibrosis. There are only a few ectatic bronchial branches deriving from the main left bronchus.

caliber and were seen to be collapsed; their opposite walls were attached to each other, although some lumen remained. In one case only a small arterial stump was found, completely collapsed and without a single arborization.

Microscopically there was extensive fibrosis of the pulmonary parenchyma.

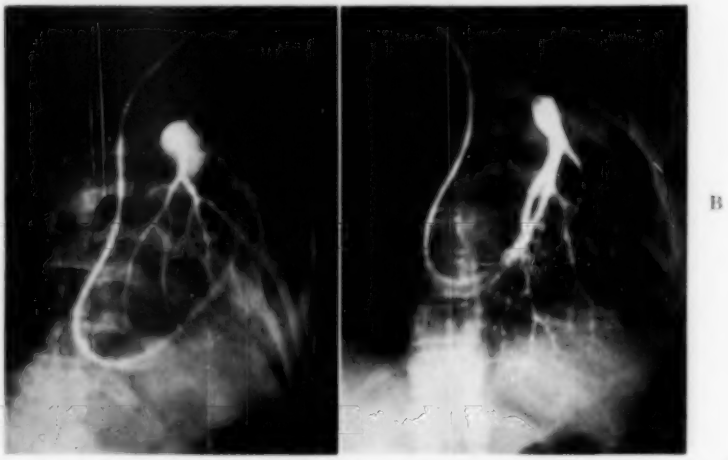

FIG. 5. *A*. E. V., a 40-year-old female patient. There is a "winter tree" image of the arterial branches in the lower lobe, demonstrated by the selective angiopneumogram. *B*. J. G., a 36-year-old female patient. There are a few thin and tortuous arterial branches revealed by the selective angiopneumography.

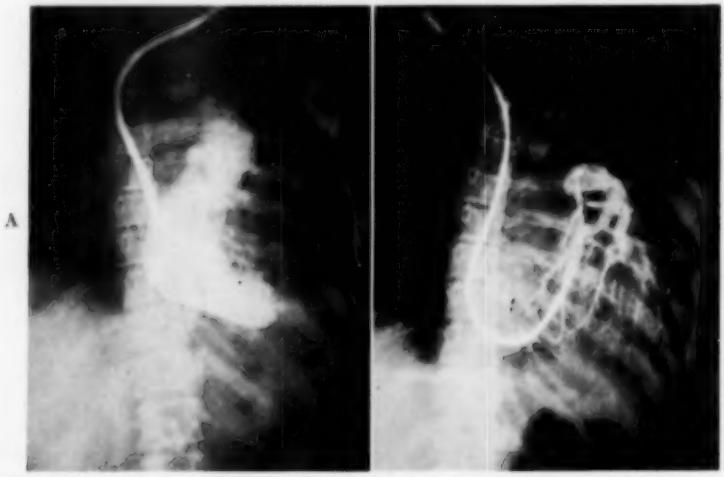

FIG. 6. M. D., a 38-year-old female patient. *A*. Global angiopneumogram. There are no arterial branches visible on the left side (May 9, 1955). *B*. Selective angiopneumogram. A few tortuous and irregular arterial branches may be seen in the lower lobe (May 13, 1955).

In 4 cases, pulmonary emphysema was present, confined to small parenchymatous sectors slightly affected by tuberculosis. In general, strong inflammatory and granulomatous infiltration with focal areas of caseous necrosis in different stages of evolution were seen.

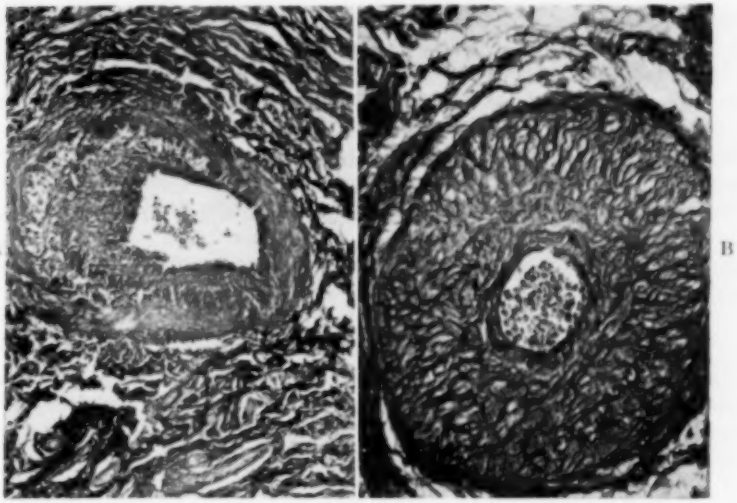

FIG. 7. *A*. Perivascular fibrosis. Eccentric proliferation of the intima. Slight hypertrophy of the muscular layer. (van Gieson stain, ×80) *B*. Diffuse proliferation of the intima, the lumen being greatly diminished. (van Gieson stain, ×320)

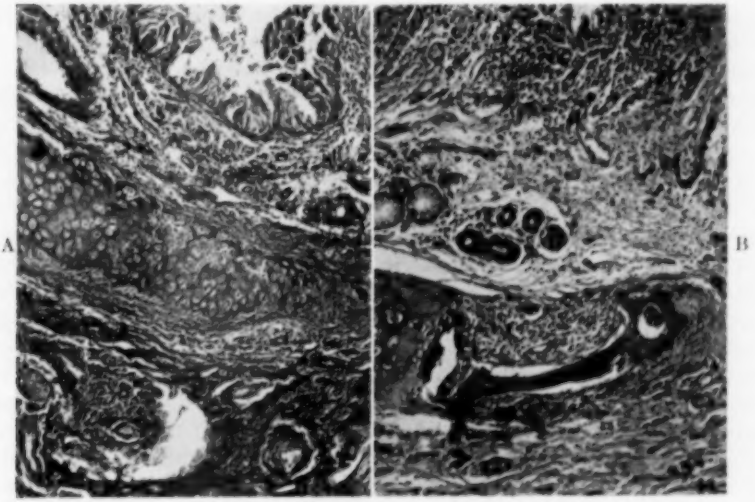

FIG. 8. *A*. Destruction of cartilage, little muscle tissue left, slight inflammatory type of infiltration. (van Gieson stain, ×80) *B*. Destruction and ossification of bronchial cartilage, little muscular tissue, dense inflammatory type of infiltration. Atrophy of the glandular tissue. (hematoxylin-eosin stain, ×80)

The more constant characteristic findings of the arterial vessels were diffuse and eccentric proliferation of the intima (figure 7*A*) and hypertrophy of the muscular layer. Less frequently, complete vascular obstruction was found in the finer vessels (figure 7*B*). In the case above mentioned the main pulmonary artery of the affected side was obstructed and no vessels could be demonstrated previously by means of angiopneumography. The angiitic changes could not be defined as specific for tuberculosis.

The bronchi showed very apparent dilatation with flabby walls and diminution or even disappearence of the muscular fibers. Inflammatory infiltration and changes of the cartilage to the point of destruction and occasionally ossification were observed (figure 8*A* and *B*).

DISCUSSION

The roentgenographic study of fibrothorax offers a wide variety of information which shows that the existing alterations are of great extent. All of the pulmonary structures are affected, the parenchyma, the vessels, the bronchi, and the pleura. Because of the marked retraction, the chest wall and the mediastinum also show changes clearly visible roentgenographically. Although the etiology of fibrothorax is multiple (cases of bronchiectasis, pneumoconiosis, scleroderma, et cetera) when it is due to tuberculosis, it shows a clear example of pathologic and extreme functional alterations as verified by histologic correlation and the study of functional tests. Such an extensive disease produces a complete physiologic deficit. The lung is excluded from the function of gaseous exchange because it does not consume oxygen, as seen in the bronchospirometric graphs. Under those circumstances the circulation through such a lung is either greatly diminished or nonexistent, as there is no healthy parenchyma left. Carlens and associates (28) had previously given a clear demonstration of the fact that, when one pulmonary artery is obstructed, the corresponding side does not consume any oxygen. In the fibrothorax, the vessels show clear hypertrophic angiitic alterations which by themselves suggest that the circulation through them must be either reduced to a minimum or completely absent. During rest the affected lung does not show any circulation as demonstrated in the global angiopneumographic plates. In these angiograms it may be seen that the contrast medium and also the blood follow the way of least resistance, although there may remain some degree of vascular permeability in the diseased lung. The selective angiopneumographic studies stress this fact. With this method a vessel which ordinarily cannot be opacified in the global angiograms can be visualized. The catheter is introduced within its lumen and the contrast medium is injected at a higher pressure than would be normal for the minor circulation. This can clearly be seen in the comparative study of global and selective angiopneumographies performed in the same patient (figure 6*A* and *B*). It is important to add that, in the cases in the present study, the pulmonary arteries were found collapsed in the resected specimens and imprisoned within the dense fibrosis. Moreover, the arteries showed hypertrophic and angiitic changes in the muscular layers. This suggests that the circulation cannot be normal in altered vessels.

The degree of pulmonary fibrosis and parenchymatous destruction explains largely the pathology of the bronchi. Many of the ectases undoubtedly were produced by retraction; others, those in which there was destruction of the bronchial cartilage, were a consequence of inflammatory processes. In the patients in whom the bronchograms showed saccular dilatations, the microscopic study revealed a predominance of fibrous lesions. In these cases the retraction was probably the determining factor of greatest importance. Where extensive destruction is present, the bronchial tree does not exist and only the cavities draining into the main bronchus are seen.

The cases of pleurogenous fibrothorax showed very few bronchial changes compared with those in which the alteration originated mainly from the parenchymal fibrosis (figure 4*A* and *B*).

The comparison of selective angiopneumographies with bronchograms clearly suggested that no correlation was possible. On the other hand, the vessels have almost constant hypertrophic angiitic alterations, while the bronchi show a great number of changes of inflammatory and destructive nature. The pathologic findings in the present study agree with those described by the majority of writers for other forms of pulmonary tuberculosis.

The age of the fibrothorax is probably the most important factor determining the roentgenographic and pathologic patterns, the oldest cases always showing the most extreme alterations. The evolution of the disease is also an important factor, since it offers the best explanation for the presence of destructive or fibrotic lesions.

SUMMARY

A roentgenographic study of 36 cases of tuberculous fibrothorax by selective angiopneumography and bronchography was made. The resected specimens from 19 of the patients who were treated by pneumonectomy were examined histologically in order to study the vascular and bronchial pathology.

Information obtained by selective angiopneumography proved that vascular permeability does exist in cases of fibrothorax and that the vessels of the affected side show profound architectural changes. These alterations cannot be visualized by global angiopneumography.

The bronchographic findings vary considerably; they are due mainly to the degree of fibrosis and pulmonary destruction, depending on the time of evolution.

There is no anatomic correlation between the angiopneumographic and the bronchographic findings in tuberculous fibrothorax.

SUMARIO

La Angioneumografía Selectiva en el Fibrotórax Tuberculoso: Comparación con la Broncografía y Correlación con los Hallazgos Histopatológicos en Pulmones Resecados Quirúrgicamente

En 36 casos de fibrotórax tuberculoso, se hizo un estudio radiográfico con la angioneumografía selectiva y la broncografía. A 19 de los enfermos que habían sido tratados con la neumonectomía se les correlacionó histológicamente a fin de estudiar la patología vascular y bronquial.

La información obtenida con la angioneumografía selectiva demostró que existe permeabilidad vascular en los casos de fibrotórax y que los vasos del lado afectado revelan profundas alteraciones en su arquitectura, alteraciones esas que no pueden visualizarse con la angioneumografía global.

Los hallazgos broncográficos varían considerablemente, debiéndose principalmente a la intensidad de la fibrosis y la destrucción pulmonar, conforme al período de evolución.

En el fibrotórax tuberculoso, no existe correlación anatómica entre los hallazgos angioneumográficos y los broncográficos.

RESUME

Angiopneumographie sélective dans le fibrothorax tuberculeux: Comparaison avec la bronchographie et corrélation avec les signes pathologiques des pièces d'exérèse pulmonaire

Une étude radiologique de 36 cas de fibrothorax tuberculeux a été effectuée par l'angiopneumographie sélective et la bronchographie. Dix-neuf des cas traités par la pneumonectomie ont été confrontés histologiquement pour l'étude de la pathologie vasculaire et bronchique.

Les renseignements fournis par l'angiopneumographie sélective ont démontré que dans le fibrothorax il existe une perméabilité vasculaire et que les vaisseaux du côté affecté présentent des altérations architecturales marquées. Ces altérations ne sont pas décelables par l'angiopneumographie globale.

Les images bronchographiques varient considérablement; ces variations dependent surtout du degré de la sclérose et de la destruction pulmonaire, selon la durée de l'évolution.

Il n'y a pas de corrélation anatomique entre les signes angiopneumographiques et bronchographiques du fibrothorax tuberculeux.

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ANTITUBERCULOUS ACTIVITY OF HINCONSTARCH, A SYNTHETIC POLYMER OF ISONIAZID, AMITHIOZONE, AND STARCH[1,2]

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INTRODUCTION

The preparation of a series of polymeric substances by the condensation of certain periodate-oxidized polysaccharides with isoniazid and *p*-aminobenzaldehyde thiosemicarbazone (amithiozone) has been described by Barry and coworkers (1, 2). They have demonstrated (3) that these compounds are effective in experimental tuberculosis of guinea pigs and mice, and O'Brien has recently reported preliminary results in the treatment of nine patients (4). Hinconstarch, the name given to the mixed polymer obtained by the condensation of oxystarch with an equimolar mixture of isoniazid and amithiozone, is estimated to contain approximately 25 per cent by weight of each of the two antituberculous agents (2).

The present report contains data relative to the activity of hinconstarch[3] in experimental tuberculosis produced by isoniazid-susceptible and -resistant bacilli in guinea pigs, mice, and rabbits. The tuberculostatic effect of the blood of guinea pigs given the drug was studied, although other *in vitro* bacteriostatic experiments were not attempted because the addition of dilute acid or alkali, which is necessary to get hinconstarch into solution, brings about decomposition of the polymer (5).

OBSERVATIONS

Protection Experiments in Mice

Mice: Sixty C57 black mice were infected intravenously with 0.3 mg. (dry weight) of virulent bovine tubercle bacilli, 30 with strain 4228-4, isoniazid-susceptible, and 30 with 4228-4, isoniazid-resistant. The latter strain, resistant to 1 but susceptible to 10 γ of isoniazid per ml. and catalase positive, was obtained from an isoniazid-treated rabbit. Previously reported experiments showed that guinea pigs infected with this strain did not respond to 15 mg. of isoniazid per kg. per day (6).

In each of these groups, 10 mice remained untreated, 10 were given hinconstarch, 0.1 per cent mixed with powdered mouse pellets, and 10 were given the drug in concentration of 0.5 per cent mixed with the diet. Treatment was started immediately after infection and continued for seventeen days. All survivors were killed on the eighty-eighth day. The results of this experiment are indicated in table 1.

It may be seen in table 1 that, in the group of mice infected with the isoniazid-susceptible strain of tubercle bacilli, 0.5 per cent of hinconstarch in the diet (approximately 1,000 mg. of drug per kg. per day) afforded good protection. All

[1] From the Trudeau Laboratory of The Trudeau-Saranac Institute, Trudeau, New York.

[2] This investigation was supported by a research grant from the National Institutes of Health, Public Health Service.

[3] The hinconstarch was generously supplied by the Nepera Chemical Co., Inc., Yonkers, New York.

TABLE 1

HINCONSTARCH IN EXPERIMENTAL MOUSE TUBERCULOSIS: INTRAVENOUS INFECTION
Drug-Diet Treatment for Seventeen Days Starting Immediately After Infection

Infecting Strain	Treatment	Survival, Days After Infection	Mortality at Days			ST_{50}	Gross Lung Disease*
			28	56	88		
Bovine 4228-4, isoniazid-susceptible	0 (Controls)	20, 21, 23, 24, 25, 25, 25, 26, 27, 27	100%	—	—	25	
	Hinconstarch 0.1%†	63, 76, 80 (7 killed at 88 days)	0	0	30%	>88	1.8
	Hinconstarch 0.5%‡	(All 10 killed at 88 days)	0	0	0	>88	1.3
Bovine 4228-4, isoniazid-resistant	0 (Controls)	17, 18, 18, 18, 20, 20, 21, 22, 25, 25	100%	—	—	20	
	Hinconstarch 0.1%	20, 21, 21, 25, 25, 27, 31, 31, 35, 39	60%	100%	—	26	
	Hinconstarch 0.5%	44, 55, 55 (7 killed at 88 days)	0	30%	30%	>88	2.5

* Average of those killed at 88 days, based on score of 0 to 4+.
† 200 mg. per kg. per day.
‡ 1,000 mg. per kg. per day.

of the 10 animals killed at eighty-eight days had gross lesions of limited extent in the lungs, however, and smears of the lungs showed occasional acid-fast bacilli. The animals given only 0.1 per cent of the drug in the diet (200 mg. per kg. per day) were protected to a lesser degree. The infection produced by the isoniazid-resistant strain was definitely less amenable to treatment, although considerable effect was noted with the higher dosage of hinconstarch.

Delayed Treatment Experiments in Guinea Pigs

Ninety guinea pigs, weighing approximately 700 gm., were infected subcutaneously in the right inguinal region with 0.1 mg. (dry weight) of tubercle bacilli, 30 each with the virulent human H37Rv strain, the bovine strain 4228-4, isoniazid-susceptible, and the 4228-4, isoniazid-resistant (the same two bovine strains used in the mouse experiment).

Treatment with hinconstarch was started twenty-eight days after infection, the drug being given by the forced feeding of one capsule daily.

It may be seen from table 2, in which the results of this experiment are presented, that the sixty-two days of treatment afforded excellent protection to the animals infected with the isoniazid-susceptible H37Rv strain and that the lower dosage of the drug (80 mg. per kg. per day) was as effective as the higher dosage of 150 mg. per kg. per day. The two bovine strains were more pathogenic than the H37Rv, both producing a 90 per cent mortality in the ninety-day period. Both the high and the low doses of hinconstarch were equally effective in the

TABLE 2

HINCONSTARCH IN EXPERIMENTAL GUINEA PIG TUBERCULOSIS: SUBCUTANEOUS INFECTION
Treatment by Capsule Once Daily Started Twenty-eight Days Later
Ten Animals in Each Group

Infecting Strain	Hinconstarch	Survival, Days After Infection	90-Day Mortality	Average Index of Tuberculosis*
	mg/day			
Human H37 Rv	0	63 (9 killed at 90 days)	10%	12.2
	55†	1 died accidentally (9 killed at 90 days)	0	3.2
	100‡	(All 10 killed at 90 days)	0	3.9
Bovine 4228-4, isoniazid-susceptible	0	46, 47, 48, 49, 53, 58, 62, 65, 79, 90(K)§	90%	—
	55	(All 10 killed at 90 days)	0	8.0
	100	One died of intercurrent infection (9 killed at 90 days)	0	8.2
Bovine 4228-4, isoniazid-resistant	0	27, 46, 51, 53, 59, 71, 71, 76, 82, 90(K)	90%	—
	55	33, 58, 65, 77, 80, 87 (4 killed at 90 days)	60%	13.2
	100	64, 67, 69 (7 killed at 90 days)	30%	12.9

* Of those animals killed at 90 days, based on scale of 0 to 4 according to amount of gross disease in each of lungs, liver, spleen, and lymph nodes (maximum total 16).

† 80 mg/kg/day.

‡ 150 mg/kg/day.

§ (K) indicates killed.

isoniazid-susceptible infection, but the treated animals killed at ninety days showed more disease than those infected with the human strain. Just as was noted in the mouse experiment, the infection produced by the isoniazid-resistant strain was less amenable to treatment but, in the guinea pigs, the higher dose of hinconstarch gave slightly better results than the lower, as indicated by a mortality of 30 per cent as against 60 per cent.

Delayed Treatment Experiments in Rabbits

The same two strains of virulent bovine tubercle bacilli were used to produce infection by the intravenous route. Three animals received 0.02 mg. (dry weight) of the isoniazid-susceptible, and 3 the same amount of the isoniazid-resistant strain. Considerable previous experience (7, 8) in this laboratory has indicated that such an infection, followed by the appearance of miliary shadows roentgenographically, is virtually 100 per cent fatal in three to seven weeks. The animals were followed by serial chest roentgenograms, and all were started on treatment three weeks later when advanced miliary disease was evident. Hinconstarch was given orally once daily, at first in capsules, and later, because of difficulty in administering the capsules, by esophageal intubation of an aqueous suspension in 2 per cent gum acacia. Dosage was started at 200 mg. a day (90 mg. per kg.) and was gradually increased to 500 mg. (160 mg. per kg.), the higher dosage being reached on the forty-sixth day of infection.

The rabbits infected with the isoniazid-susceptible organisms showed a slow progressive clearing of the lung lesions after treatment was started, but there were still many residual shadows visible on the roentgenograms just before the animals were sacrificed after sixty-seven days of treatment. Autopsy of these animals revealed the presence of gross tuberculous lesions of limited extent in the lungs,

spleen, and kidneys. This type of response, while indicative of a definite therapeutic effect, is much less dramatic than that usually seen with full doses of streptomycin, viomycin, or isoniazid (7).

The rabbits infected with the isoniazid-resistant strain showed no significant response to treatment except perhaps a slight prolongation of life. No clearing of the disease roentgenographically was noted, and all 3 animals died with progressive tuberculosis in thirty-five to sixty-three days after infection.

Bacteriostatic Effect of Serum from Hinconstarch-Fed Guinea Pigs

Six normal guinea pigs were each given one capsule containing 100 mg. of hinconstarch (150 mg. per kg.), and blood was removed from the hearts at one and one-quarter and three hours. Serial twofold dilutions of the pooled sera were made in duplicate into tubes of Tween*-albumin medium, and the growth-inhibitory activity was tested against strains H37Rv, H37Rv resistant to isoniazid, and H37Rv resistant to amithiozone. The three-hour samples showed slightly greater activity than the earlier ones. Against the H37Rv strain, the eightfold dilution gave partial inhibition, and the fourfold prevented growth for fourteen days. The isoniazid-resistant strain was only partially inhibited by the four- and twofold dilutions, while the amithiozone-resistant strain was unable to grow in the medium containing a fourfold serum dilution. When these results are compared with those of similar tests using normal guinea pig serum with known concentrations of isoniazid-amithiozone, they indicate that the observed pattern of growth inhibition corresponds to that of serum containing approximately 2 γ of each drug per ml. These data will be reported in greater detail elsewhere.

Chemical assay of the same pooled sera for isoniazid activity by the cyanogen bromide method gave average results of 1.2 γ per ml. for the one and one-quarter- and 2.8 γ for the three-hour sample. It was determined that amithiozone did not interfere with this assay, but preliminary attempts at chemical determination of thiosemicarbazone activity were unsuccessful.

DISCUSSION

The results of the mouse experiment differ only slightly from those reported by Barry and associates (3), who obtained maximum increase in median survival time with 268 mg. of hinconstarch per kg. per day in the isoniazid-resistant infection. It was found in the experiments reported herein that it was necessary to give more than 200 mg. per kg. per day to obtain maximum benefit in the isoniazid-susceptible infection and that, even with 1,000 mg. per kg., animals infected with the isoniazid-resistant strain showed a 30 per cent mortality at fifty-six days.

Unfortunately, the results obtained in guinea pigs cannot be compared because the isoniazid-resistant strain used by Barry and co-workers had little pathogenicity for guinea pigs. The data reported herein show that, in animals infected with the isoniazid-susceptible bovine strain, increasing the dosage of hinconstarch from 80 to 150 mg. per kg. per day produced no increase in benefit and

that the results obtained were inferior to those usually seen in this laboratory in similar infections treated with 15 mg. of isoniazid per kg. per day (8). The response with 150 mg. of hinconstarch per kg. per day in the isoniazid-resistant infection was probably not maximal, and higher dosage might have given better results. In the more benign infection produced by the H37Rv organisms, the drug at 80 mg. per kg. per day produced excellent results, similar to those usually noted with 5 to 15 mg. per kg. per day of isoniazid (9), but these results were not improved by almost doubling the dose.

The intravenous infection of rabbits with highly virulent bovine tubercle bacilli is a very stringent test for an antituberculous drug. The relatively poor results reported herein may be due in part to the difficulty encountered in the administration of the drug during the first three weeks of treatment. After that time, however, a fairly uniform dosage of 160 mg. per kg. per day was maintained. The response of the isoniazid-susceptible infection to this dosage was not as rapid or complete as that usually seen with 14 mg. of isoniazid per kg. per day (7, 8). Here again, it is possible that a higher dosage of hinconstarch would be more effective. Since no toxic effects were noted in any of the treated animals, further experiments in mice and guinea pigs are under way, using larger amounts of hinconstarch.

The question naturally arises whether the *in vivo* activity of this drug might be due completely to the isoniazid and amithiozone molecules which might be split off somewhere in the body. This can be answered only by further investigation, including chemical determinations of the two drugs and their metabolic products in the blood and tissues of hinconstarch-treated animals and man. Then similar results should be obtained by the administration of comparable amounts of isoniazid and amithiozone together. The results of the preliminary determinations of the tuberculostatic activity of the serum from hinconstarch-treated guinea pigs are consistent with the hypothesis that significant degradation of hinconstarch occurs *in vivo*. Normal serum to which was added 2 γ of isoniazid per ml., either alone or in combination with an equal amount of amithiozone, exhibited much the same pattern of growth inhibition as the test serum. Barry and associates (10) have reported on the *in vitro* and *in vivo* activity of isoniazid and amithiozone, alone and in combination, against isoniazid-susceptible and -resistant organisms, but the only experiment reported by these workers in which these drugs were used concurrently with hinconstarch was complicated by the lack of pathogenicity of the isoniazid-resistant bacilli (3).

The value of a drug such as hinconstarch would seem to depend on two factors: decreased toxicity and activity against isoniazid-resistant infections. The former can be determined only by cautious administration of the drug to patients. The acute oral lethal dose (LD_{50}) for mice has been reported to be more than 8,000 mg. per kg. (3), in contrast to the 140 to 200 mg. per kg. of isoniazid. The lowering of isoniazid toxicity has been confirmed in this laboratory during prolonged feeding experiments in which mice tolerated 2,000 mg. of hinconstarch, but were killed by 500 mg. of isoniazid per kg. per day mixed with the diet. It will be re-

called that isoniazid constitutes approximately 25 per cent by weight of the hinconstarch molecule. This reduction in toxicity might be due to decreased absorption or to conversion of the isoniazid into other metabolic derivatives which may be less active biologically as well as less toxic.

With respect to its activity against isoniazid-resistant infections, it is obvious that, even with a two- to fivefold increase in dosage, hinconstarch has much less effect in experimental infections caused by resistant organisms than in those produced by isoniazid-susceptible strains. This is not surprising since the more active half of its therapeutic component is isoniazid. The drug may be beneficial even under these circumstances, however, if a large enough dose can be given without toxicity.

SUMMARY

Hinconstarch, a new synthetic polymer of starch, isoniazid, and amithiozone, was administered to guinea pigs, mice, and rabbits with experimental tuberculosis produced by isoniazid-susceptible and -resistant strains. Oral administration of the drug produced a good effect in the isoniazid-susceptible infections in dosages of 200 to 1,000 mg. per kg. per day for mice, 80 mg. per kg. for guinea pigs, and 160 mg. per kg. for rabbits. The infections produced by the isoniazid-resistant strain were less amenable to hinconstarch. Rabbits showed only negligible benefit from 160 mg. per kg. per day; guinea pigs exhibited a limited response to 150 mg. per kg., but higher dosage is being investigated; and mice responded fairly well to 1,000 mg. per kg. The effects noted were probably not the maximal ones attainable, and higher dosage is being tried.

The serum of guinea pigs given a single 100 mg. capsule inhibited the growth of the H37Rv strain and its isoniazid- and amithiozone-resistant substrains in the same pattern as that of normal serum containing approximately 2 γ each of isoniazid and amithiozone per ml.

SUMARIO

Actividad Antituberculosa del Hinconstarch, Producto Sintético de la Isoniacida, la Amitiozona y el Almidón

El hinconstarch, nuevo polímero sintético del almidon, de la isoniacida y la amitiozona, fué administrado a cobayos, ratones y conejos con tuberculosis experimental producida por cepas isoniazido-susceptibles y resistentes. La administración oral de la droga produjo buen efecto en las infecciones isoniacido-susceptibles a dosis de 200 a 1,000 mgs. por kg. al día para los ratones, de 80 mgs. por kg. para los cobayos y 160 mgs. por kg. para los conejos. Las infecciones producidas por la cepa isoniacido-resistente fueron menos sumisas al hinconstarch. Los conejos no mostraron más que beneficio menospreciable con 160 mgs. por kg. al día, los cobayos manifestaron una respuesta limitada a 150 mgs. por kg., pero se investigan ahora dosis más altas, y los ratones respondieron bastante bien a 1,000 mgs. por kg. Los efectos notados no fueron probablemente los máximos obtenibles y se están ensayando dosis más altas.

El suero de los cobayos que recibieron una sola cápsula de 100 mgs. inhibió el desarrollo de la cepa H37Rv y las subcepas isoniacido-y-amitiozono-resistentes en la misma forma que el suero normal que contiene aproximadamente 2γ, cada uno, de isoniacida y amitiozona por ml.

RESUME

Activité antituberculeuse de l'hinconstarch, produit synthétique dérivé de l'isoniazide, del' amithiozone et de l'amidon

L'hinconstarch, nouveau polymère synthétique dérivé de l'amidon de l'isoniazide et de l'amithiozone, a été administré à des cobayes, souris et lapins atteints de tuberculose expérimentale produite par des souches isoniazide-sensibles et isoniazide-résistantes. L'administration buccale du composé a produit un effet satisfaisant dans les infections isoniazides-sensibles aux doses de 200 à 1.000 mg/kg par jour chez la souris, 80 mg/kg chez le cobaye et 160 mg/kg chez le lapin. Les infections produites par la souche isoniazide-résistante étaient moins sensibles à l'action de l'hinconstarch. Chez les lapins l'amélioration a été négligeable avec l'administration de 160 mg/kg par jour; les cobayes ont réagi de façon limitée à 150 mg/kg, mais des recherches relatives à des doses plus élevées sont en cours. Les souris ont assez bien réagi à 1.000 mg/kg. Les effets enregistrés ne representaient probablement pas le maximum susceptible d'être atteint et l'administration de doses plus élevées est actuellement essayée.

Le sérum des cobayes recevant une seule capsule dosée à 100 mg inhibait le développement de la souche H37Rv et ses sous-souches isoniazide- et amithiozone-résistantes, de la même maniere qu'avec un sérum normal renfermant approximativement 2γ d'isoniazide et 2γ d'amithiozone par ml.

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THE PLACE OF RESECTION IN THE MANAGEMENT OF PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

In the relatively short period since the general introduction of streptomycin in the therapy of pulmonary tuberculosis in 1947, along with the many important refinements in chemotherapy since that time (1), pulmonary resection has become the most popular and effective method of surgical therapy. It has been safely and successfully employed in the widely varying forms of the disease (2–11). Effective drug therapy, the very means which allowed the safe use of resection as it is known today, has revolutionized the medical as well as the surgical management of the disease. Indeed, the profound influence and the apparent success of long-term drug therapy on the course and treatment of tuberculosis has raised to a considerable extent the real question of the need for resection.

The purposes of the present report are several. The results of a study of 226 resection cases will be reported, and this will serve to emphasize the various factors which influence the success of resection. Among these factors are the preoperative and postoperative drug therapy, the indication for operation, the extent of disease, and the type of resection. The shortcomings and hazards of resection in certain instances will be discussed and remedies suggested. The criteria for the use of resection in patients with small residual lesions are subjected to extensive examination.

CASE MATERIAL

The resections were done by or under the direction of two of the writers (E.C.D. and G.R.M.) in association with successive Residents in Thoracic Surgery at the University of Virginia Hospital.

The 226 resection cases to be reported are divided into two groups: *Group 1* consists of 106 patients discharged from Blue Ridge Sanatorium between 1949 and June, 1952; *Group 2* consists of 120 patients discharged from the sanatorium between July, 1952, and June, 1953.

OBSERVATIONS

A summary of the cases is presented in table 1. There was a considerably larger number of patients in *Group 1* with far advanced tuberculous disease than in *Group 2*. Moreover, in *Group 1* there was a larger number of patients in whom the indications for operation were destroyed lung, bronchial stenosis,

[1] From the Blue Ridge Sanatorium; Department of Thoracic Surgery, University of Virginia School of Medicine; and Department of Surgery, University of Virginia School of Medicine, Charlottesville, Virginia.

TABLE 1

SUMMARY OF THE CASES

	Total		Group 1		Group 2	
Number of Cases	226		106		120	
Number of Resections	232		108		124	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Age range						
10–19 years	21	9.0	9	8.5	12	10.0
20–39 years	148	65.5	72	67.9	76	63.3
40–49 years	41	18.1	17	16.0	24	20.0
50 years and older	16	7.1	8	7.5	8	6.7
Sex						
Male	80	35.4	38	35.8	42	35.0
Female	146	64.6	68	64.2	78	65.0
Indication for operation						
Upper lobe cavity	57	25.2	21	18.9	36	30.0
Upper lobe "closed" lesion	50	22.2	16	15.1	34	28.3
Lower lobe cavity	37	16.4	24	22.6	13	10.8
Lower lobe "closed" lesion	12	5.3	2	1.9	10	8.3
Thoracoplasty failure	23	10.2	14	13.2	9	7.5
Destroyed lung	15	6.6	13	12.3	2	1.7
Destroyed lobe	11	4.9	4	3.8	7	5.8
Bronchial stenosis	10	4.4	9	8.5	1	0.8
Other	11	4.9	3	2.8	8	6.7
Original extent of disease						
Minimal	14	6.2	6	5.6	8	6.7
Moderately advanced	130	57.5	50	47.2	80	66.7
Far advanced	82	36.3	50	47.2	32	26.7
Type of resection						
Pneumonectomy	37	16.4	29	27.4	8	6.7
Lobectomy	78	34.5	36	34.0	42	35.0
Segmental resection	65	28.8	16	15.1	49	40.8
Wedge resection	46	20.4	25	23.6	21	17.5
Preoperative streptomycin						
None*	46	20.4	37	35.0	9	7.5
Less than 2 months	63	27.9	53	50.0	10	8.3
More than 2 months	40	17.7	11	10.4	29	24.2
More than 4 months	31	13.7	5	4.7	26	21.7
More than 6 months	46	20.4	0		46	38.3

* Includes 14 patients in whom the amount of preoperative streptomycin given was unknown; however they probably received none.

and thoracoplasty failure. The patients in *Group 1* generally received inadequate or no preoperative drug therapy as compared to the patients in *Group 2*, to whom adequate preoperative therapy was administered.

Both of these circumstances, the greater extent of disease and more serious disease, and the relatively inadequate preoperative drug therapy favored the higher incidence of tuberculous complications in the *Group 1* cases which may be noted in table 1.

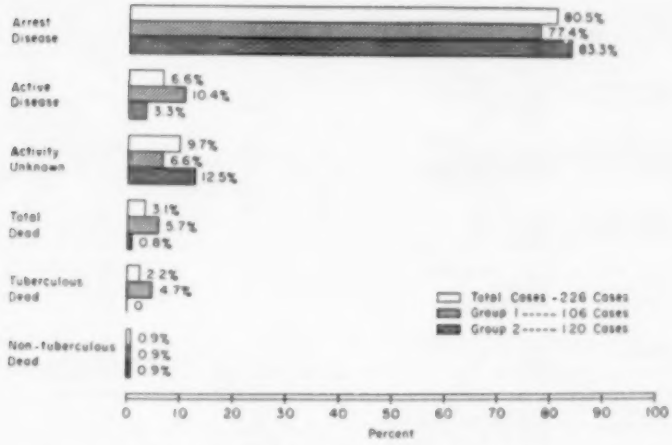

FIG. 1. Results of treatment (December, 1953).

Results of resection: The data shown in figure 1 were compiled in December, 1953, six months after the discharge of the more recent group of patients. At that time, 80 per cent of all of the patients had arrested tuberculous disease. Not a single death resulting from tuberculosis occurred among the patients in *Group 2* as compared with 4.7 per cent of tuberculous deaths among the *Group 1* patients. The case fatality from all causes was 3.1 per cent.

Complications of resection: Complications which occurred within twelve months of the time of resection are shown in figure 2. The majority of the complications developed within thirty days of the time of resection.

Tuberculous complications occurred three times as often among the patients in *Group 1*. The same fact is expressed in the higher incidence of spread and exacerbation of the disease among these patients.

Bronchopleural fistula occurred in 7.5 per cent of both the *Group 1* and *Group 2* patients. The sequelae of bronchopleural fistula in the *Group 1* cases were very serious. In the majority of the cases, tuberculous empyema and spread of disease were associated with the fistula. Not a single tuberculous empyema and not a single instance of spread of disease occurred in the *Group 2* patients with bronchopleural fistula.

The relatively high incidence of "lung leaks," also referred to as "air leaks," "delayed re-expansion," "air space," and what the present writers designate "small bronchopleural fistula" is notable. Residual air spaces of significant size which persisted for four weeks, despite repeated aspiration, were taken as evidence of lung leaks and were so reported (12). In such cases, the leakage of air, usually from the lung tissue or from very small bronchi, is very slight. The patient is usually well and empyema is uncommon, in contrast to the situation with a large bronchopleural fistula. It is recognized that the presence of residual air spaces may be caused by factors other than the leakage of air, such as post-

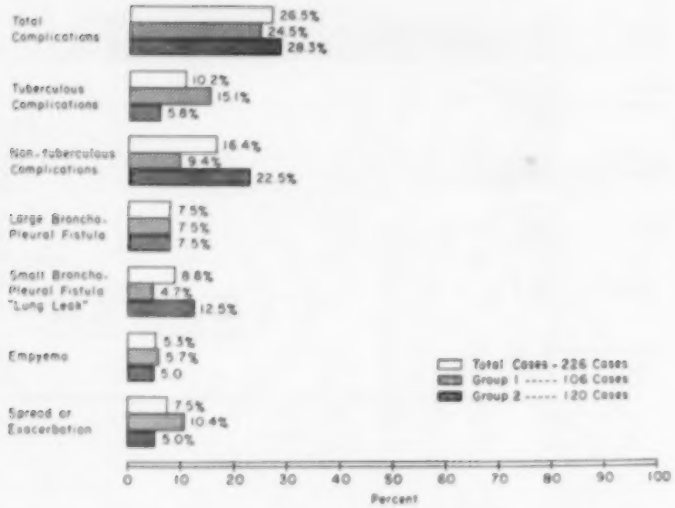

FIG. 2. Complications within twelve months after resection.

operative atelectasis, organizing hemothorax, and inadequate pulmonary tissue to fill the bony hemithorax. Although lung leaks are not in themselves of great significance, thoracoplasty is often required to obliterate the pleural space, as shown in table 2*A*.

As may be seen in table 2*B*, the majority of patients who developed complications recovered satisfactorily. The exception to this was the course in the patients who developed tuberculous complications, and most of these were in *Group 1*.

Factors which influence the incidence and nature of complications: Preoperative chemotherapy: The influence of preoperative chemotherapy and its duration are

TABLE 2 *A*

BRONCHOPLEURAL FISTULA

	Number of Cases	Type of Fistula	
		Large	Small*
Total cases	37	17	20
Spontaneous closure	9 (24.3%)	2 (11.8%)	7 (35.0%)
Closure with catheter	2 (5.4%)	1 (5.9%)	1 (5.0%)
Decortication or thoracoplasty	20 (54.1%)	8 (47.1%)	12 (60.0%)
Uncontrolled fistula	3 (8.1%)	3 (17.6%)	0
Dead†	3 (8.1%)	3 (17.6%)	0

* "Small" is equivalent to the term "lung leak."

† All 3 patients had tuberculous complications (*Group 1*).

TABLE 2 *B*

FATE OF PATIENTS WITH COMPLICATIONS

	Number of Patients	Satisfactory Result Therapy*	Unsatisfactory Result Therapy†	Dead	Fate Unknown
Tuberculous complications‡	23	10 (43.5%)	7 (30.4%)	4 (17.5%)	2 (8.7%)
Nontuberculous complications	37	30 (81.1%)	2 (5.4%)	1 (2.7%)	4 (10.8%)

* Refers to arrest of disease in patients with tuberculous complications.

† Refers to active disease in patients with tuberculous complications.

‡ *Group 1:* 16 patients; *Group 2:* 7 patients.

clearly shown in figure 3. As pointed out previously, the *Group 1* patients did not receive adequate preoperative drug therapy and the resulting relationship to the incidence of tuberculous complications is evident. In contrast, the *Group 2* patients received reasonably adequate preoperative drug therapy and the lower incidence of tuberculous complications is striking. When the incidence of tuberculous complications was compared for the patients who did and those who did not receive adequate preoperative drug therapy, the results were as follows:

	Tuberculous Complications in Per Cent
109 patients received none or less than two months of chemotherapy	20.2
117 patients received more than two months of chemotherapy	1.7

In short, tuberculous complications were more than ten times as common among the patients whose preoperative chemotherapy was theoretically inadequate than among those whose preoperative therapy was adequate.

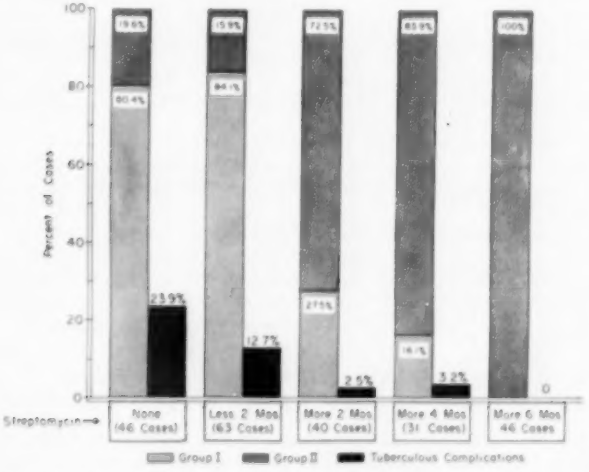

FIG. 3. Preoperative streptomycin: relationship to immediate tuberculous complications.

TABLE 3

PREOPERATIVE STREPTOMYCIN: RELATIONSHIP TO THE TYPE OF RESECTION

Type of Resection	Number of Cases	Amount of Preoperative Streptomycin				
		None*	Less Than 2 Months	More Than 2 Months	More Than 4 Months	More Than 6 Months
Pneumonectomy	37	18 (48.6%)	11 (29.7%)	6 (16.2%)	1 (2.7%)	1 (2.7%)
Lobectomy	78	17 (21.8%)	23 (29.5%)	10 (12.8%)	11 (14.1%)	17 (21.8%)
Segmental resection	65	4 (6.2%)	10 (15.4%)	19 (29.2%)	12 (18.5%)	20 (30.8%)
Wedge resection	46	7 (15.2%)	19 (41.3%)	5 (10.9%)	7 (15.2%)	8 (17.4%)
Total	226	46 (20.4%)	63 (27.9%)	40 (17.7%)	31 (13.7%)	46 (20.4%)

* Includes 14 patients in whom the amount of preoperative streptomycin given was unknown; however they probably received none.

It is true that many of the patients who did not receive adequate preoperative drug therapy had extensive disease which required pneumonectomy (table 3). When the *Group 1* lobectomy patients who did not receive adequate chemotherapy are compared with the *Group 2* lobectomy patients who received such therapy, it is found that tuberculous complications occurred in 19.2 per cent of *Group 1* lobectomy patients in contrast to a 4.8 per cent incidence in the *Group 2* lobectomy patients (table 6). This is perhaps a more correct statement of the influence of preoperative drug therapy on the incidence of tuberculous complications, as the factor of the extent of disease was better controlled.

The influence of preoperative drug therapy is reflected in the results of other considerations, namely, the indication for operation, extent of disease, contralateral disease, and the type of resection, and their relationship to the incidence

TABLE 4

INDICATION FOR OPERATION: RELATIONSHIP TO THE INCIDENCE OF COMPLICATIONS

Indication for Operation*	Total Number of Cases	Group 1	Group 2	Total Complications	Tuberculous Complications
Upper lobe cavity	57	21 (36.8%)	36 (63.2%)	12 (21.1%)	3 (5.3%)
Upper lobe "closed" lesion	50	16 (32.0%)	34 (68.0%)	10 (20.0%)	2 (4.0%)
Lower lobe cavity	37	24 (64.9%)	13 (35.1%)	16 (43.2%)	6 (16.2%)
Lower lobe "closed" lesion	12	2 (16.7%)	10 (83.3%)	1 (8.3%)	0
Thoracoplasty failure	23	14 (60.9%)	9 (39.1%)	7 (30.4%)	4 (17.4%)
Destroyed lung	15	13 (86.7%)	2 (13.3%)	5 (33.3%)	5 (33.3%)
Destroyed lobe	11	4 (36.4%)	7 (63.6%)	2 (18.2%)	1 (9.1%)
Bronchial stenosis	10	9 (90.0%)	1 (10.0%)	2 (20.0%)	0
Other	11	3 (27.3%)	8 (72.7%)	5 (45.5%)	2 (18.2%)
Total	226	106 (46.9%)	120 (53.1%)	60 (26.5%)	23 (10.2%)

* More than one indication for operation may have existed; for example, destroyed lung, destroyed lobe, thoracoplasty failure, and bronchial stenosis were often associated indications for operation.

TABLE 5 *A*

EXTENT OF DISEASE AT THE TIME OF RESECTION: RELATIONSHIP TO THE INCIDENCE OF COMPLICATIONS

Extent of Disease*	Group 1			Group 2		
	Number of Cases	Complications		Number of Cases	Complications	
		Total Complications	Tuberculous Complications		Total Complications	Tuberculous Complications
Minimal						
Unilateral disease	6	1	1	7	0	0
Bilateral disease*	1	0	0	4	1	0
Moderately advanced						
Unilateral disease	22	4 (18.2%)	2 (9.1%)	14	5 (35.7%)	0
Bilateral disease*	49	10 (20.4%)	5 (10.2%)	82	23 (28.0%)	5 (6.1%)
Far advanced						
Unilateral disease	3	2	1	0		
Bilateral disease*	25	9 (36.0%)	7 (28.0%)	13	5 (38.5%)	2 (15.4%)
Total	106	26 (24.5%)	16 (15.1%)	120	34 (28.3%)	7 (5.8%)

* "Bilateral" disease refers only to the presence of disease on both sides and not to its extent on either side.

TABLE 5 *B*

CONTRALATERAL DISEASE: RELATIONSHIP TO SPREAD OR EXACERBATION

Extent of Contralateral Disease*	Group 1			Group 2		
	Number of Cases	Spread or Exacerbation		Number of Cases	Spread or Exacerbation	
		Immediate†	Late‡		Immediate†	Late‡
None	26	3 (11.5%)	0	22	2 (9.1%)	0
"Minimal"	51	4 (7.8%)	6 (11.8%)	72	0	1 (1.4%)
"Moderately advanced"	15	0	1 (6.7%)	22	0	0
"Far advanced"	0			0		
Unknown	14	1	1	4	1	0
Total†, ‡	106	8 (7.5%)	8 (7.5%)	120	3 (2.5%)	1 (0.8%)

* The terms "minimal" et cetera, do not have the accepted meaning, and refer *only* to the contralateral disease.

† Refers to spread or exacerbation occurring within thirty days of the time of resection. Excludes 4 cases of ipsilateral spread or exacerbation.

‡ Refers to spread or exacerbation occurring more than thirty days following resection: the vast majority were noted more than twelve months following resection. Excludes 5 cases of ipsilateral spread or exacerbation.

and nature of complications. The proportion of *Group 1* and *Group 2* cases is a guide to the factor of drug therapy, and that proportion is noted in the additional data to be presented (figure 3).

Indications for operation: The indication for operation is generally related closely to the extent of the disease. Thus destroyed lung, giant cavity, destroyed

TABLE 6

COMPLICATIONS WITHIN TWELVE MONTHS OF RESECTION

Type of Resection	Number of Cases	Cases with Complications	Tuberculous Complications*	Nontuberculous Complications	Type of Complication						
					Spread or Exacerbation†	Bronchopleural Fistula		Empyema§	Bronchial Stump Ulcer	Tuberculous Wound Infection	Other
						Small‡	Large				
Group 1											
Pneumonectomy	29	8 (27.6%)	7 (24.1%)	1 (3.4%)	5 (17.2%)	0	1 (3.4%)	1 (3.4%)	2(6.9%)	0	0
Lobectomy	36	12 (33.3%)	7 (19.4%)	5 (13.9%)	4 (11.1%)	4 (11.1%)	6 (16.7%)	5 (13.9%)	1(2.8%)	2(5.6%)	0
Segmental resection	16	4 (25.0%)	0	4 (25.0%)	0	1 (6.3%)	1 (6.3%)	0	0	0	2(12.5%)
Wedge resection	25	2 (8.0%)	2 (8.0%)	0	2 (8.0%)	0	0	0	0	0	0
Total, *Group 1*	106	26 (24.5%)	16 (15.1%)	10 (9.4%)	11 (10.4%)	5 (4.7%)	8 (7.5%)	6 (5.7%)	3(2.8%)	2(1.9%)	2(1.9%)
Group 2											
Pneumonectomy	8	5 (62.5%)	3 (37.5%)	2 (25.0%)	3 (37.5%)	0	1 (12.5%)	1 (12.5%)	0	0	1(12.5%)
Lobectomy	42	14 (33.3%)	2 (4.8%)	12 (28.6%)	1 (2.4%)	9 (21.4%)	3 (7.1%)	2 (4.8%)	1(2.4%)	0	0
Segmental resection	49	14 (28.6%)	1 (2.0%)	13 (26.5%)	1 (2.0%)	6 (12.2%)	5 (10.2%)	3 (6.1%)	0	0	3(6.1%)
Wedge resection	21	1 (4.8%)	1 (4.8%)	0	1 (4.8%)	0	0	0	0	0	0
Total, *Group 2*	120	34 (28.3%)	7 (5.8%)	27 (22.5%)	6 (5.0%)	15 (12.5%)	9 (7.5%)	6 (5.0%)	1(0.8%)	0	4(3.3%)
Total, All Cases	226	60 (26.5%)	23 (10.2%)	37 (16.4%)	17 (7.5%)	20 (8.8%)	17 (7.5%)	12 (5.3%)	4(1.8%)	2(0.9%)	6(2.7%)

* Tuberculous complications noted more than six months after resection in 8 cases.

† Spread or exacerbation noted more than six months after resection in 5 cases.

‡ "Small" is equivalent to the term "lung leak."

§ Tuberculous empyema in 5 cases (all *Group 1* cases).

lobe, thoracoplasty failure, and bronchial disease mean extensive disease, and the tuberculous complications of the appropriate resection procedure (pneumonectomy as a rule) are usually many (table 4).

The incidence of tuberculous complications was about the same in resection of upper lobe cavities and closed lesions, and the proportion was the same in each group. Resection of lower lobe cavities was apparently associated with a higher incidence of tuberculous complications than lower lobe closed lesions. It should be noted, however, that the majority of patients with lower lobe cavities were in *Group 1* and had received inadequate or no preoperative drug therapy.

Extent of disease and contralateral disease: The extent of disease and its relationship to the incidence of tuberculous complications is presented in table 5*A*. The connection between the extent of contralateral disease and the occurrence of contralateral spread or exacerbation is presented in table 5*B*. The meaning of these results is partly obscured by the more important consideration of preoperative drug therapy.

Type of resection: The type of resection follows in turn from the indication for operation and the extent of disease. The relationship of the type of resection and the incidence and nature of complications is shown in table 6. Pneumonectomy was easily the most hazardous of all resections, as noted previously. Lobectomy was associated with a slightly higher incidence of tuberculous complications than segmental resection (because of the tuberculous complications among *Group 1* lobectomy cases); but otherwise the complications of lobectomy and segmental resection were similar. Wedge resection was associated with strikingly few complications of any kind, and there were no bronchopleural fistulas or lung leaks following this resection.

TABLE 7

PNEUMONECTOMY: MISCELLANEOUS DATA

	Total Cases	Group 1	Group 2	Total Complications	Tuberculous Complications	Spread or Exacerbation	Bronchopleural, Fistula	Empyema
Right versus left pneumonectomy								
Right pneumonectomy	12	10	2	4 (33.3%)	4 (33.3%)	4 (33.3%)	1 (8.3%)	1 (8.3%)
Left pneumonectomy	25	19	6	9 (36.0%)	6 (24.0%)	2 (8.0%)	1 (4.0%)	1 (4.0%)
Stenotic main stem bronchus*								
Stenosis right main stem	3	3	0	1	1	1	0	0
Stenosis left main stem	12	10	2	3 (25.0%)	3 (25.0%)	2 (16.7%)	0	0
Pre-resection thoracoplasty								
Thoracoplasty	15	11	4	5 (33.3%)	2 (13.8%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
No thoracoplasty	22	18	4	8 (36.4%)	8 (36.4%)	7 (31.8%)	1 (4.5%)	1 (4.5%)

* Stenosis here refers to stenosis of more than 50% of the main stem bronchus.

TABLE 8

LOBECTOMY: MISCELLANEOUS DATA

	Number of Cases	Group 1	Group 2	Total Complications	Tuberculous Complications	Bronchopleural Fistula		Empyema	Spread or Exacerbation
						Large	Small*		
Type of lobectomy									
Right upper lobectomy	41	18	23	13 (30.7%)	5 (12.2%)	4 (9.8%)	7 (17.1%)	4 (9.8%)	2 (4.9%)
Right lower lobectomy	14	7	7	4 (28.6%)	2 (14.3%)	4 (28.6%)	0	2 (14.3%)	2 (14.3%)
Left upper lobectomy	13	8	5	4 (30.8%)	1 (7.8%)	0	3 (23.1%)	0	0
Left lower lobectomy	5	2	3	4	0	1	3	1	0
Middle and lower lobectomy	5	1	4	1	1	0	0	0	1
Pre-resection thoracoplasty†									
Thoracoplasty	13	5	8	3 (23.1%)	3 (23.1%)	1 (7.8%)	0	1 (7.8%)	1 (7.8%)
No thoracoplasty	46	22	24	15 (32.8%)	4 (8.7%)	3 (6.5%)	10 (21.7%)	2 (4.3%)	1 (2.1%)
Pre-resection pneumoperitoneum, upper lobectomy									
Pneumoperitoneum	13	2	11	—	—	0	2 (15.4%)	—	—
No pneumoperitoneum	42	24	18	—	—	4 (9.5%)	9 (21.4%)	—	—
Pre-resection pneumoperitoneum, lower lobectomy									
Pneumoperitoneum	7	3	4	—	—	1	0	—	—
No pneumoperitoneum	11	6	5	—	—	4 (36.4%)	2 (18.2%)	—	—

* "Small" is equivalent to the term "lung leak."

† Lower lobectomy cases excluded. The thoracoplasty group includes 2 upper and middle lobectomy cases with one complication; and the no thoracoplasty group includes 3 upper and middle lobectomy cases with no complications.

TABLE 9

TUBERCULOUS BRONCHITIS: RELATIONSHIP TO THE INCIDENCE OF BRONCHOPLEURAL FISTULA AND BRONCHIAL STUMP ULCER*

Tuberculous Bronchitis	Number of Cases	Tuberculous Complications	Bronchopleural Fistula		Bronchial Stump Ulcer
			Large	Small†	
Present‡	54	9 (16.7%)	2 (3.7%)	4 (7.4%)	3 (5.6%)
Absent	83	6 (7.3%)	12 (14.5%)	9 (10.8%)	1 (1.2%)
No data§	43	6 (14.0%)	3 (7.0%)	7 (16.3%)	0
Total*	180	21 (11.7%)	17 (9.4%)	20 (11.1%)	4 (2.2%)

* Excludes 46 cases of wedge resection.
† "Small" is equivalent to the term "lung leak."
‡ Bronchitis was present at some time during treatment.
§ No report of bronchoscopic examination.

TABLE 10 *A*

FOLLOW-UP OBSERVATIONS (DECEMBER, 1953)

Lapse of Time after Resection	Group 1		Group 2	
	Number of Cases	Cases Followed	Number of Cases	Cases Followed
12 to 17 months	0	0	40	24
18 to 23 months	11	7	70	47
24 to 35 months	74	60	8	3
36 to 48 months	15	14	1	1
Dead	6	6	1	1
Total	106	87 (82.1%)	120	76 (63.3%)

TABLE 10 *B*

RESULTS OF FOLLOW-UP OBSERVATIONS*

	Group 1 (106 Cases)		Group 2 (120 Cases)	
	Exacerbation	Dead†	Exacerbation	Dead†
Number of cases	11 (10.4%)	1 (0.9%)	1 (0.8%)	1 (0.8%)
Type of resection				
Pneumonectomy	5	1	0	0
Lobectomy	2	0	0	0
Segmental resection	2	0	1	1
Wedge resection	2	0	0	0
Time of relapse or death‡				
12 to 17 months	5	1	1	1
18 to 24 months	6	0	0	0

* Refers to follow-up more than twelve months following the date of resection.
† *Group 1:* Exacerbation of disease the cause of death in one patient. *Group 2:* Cor pulmonale the cause of death in one patient with inactive tuberculosis.
‡ Time of relapse or death following the date of resection.

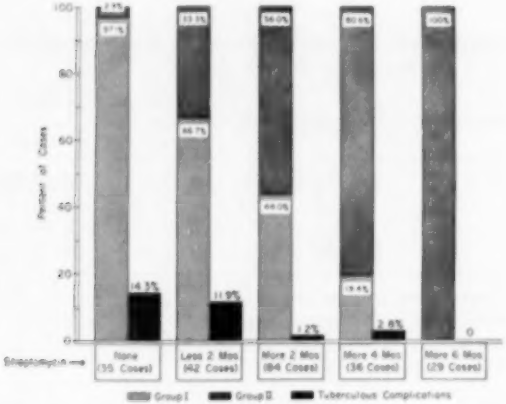

FIG. 4. Postoperative streptomycin: relationship to late tuberculous complications.

Pneumonectomy: The data in table 7 show that right pneumonectomy was questionably associated with a higher incidence of spread and exacerbation of disease than was the case with left pneumonectomy. The same relationship was seen in patients who did and did not have a pre-resection thoracoplasty, for the great majority of the patients who had left pneumonectomy had had a previous thoracoplasty, whereas only a few of the patients with right pneumonectomy had had a previous thoracoplasty.

TABLE 11

RESULTS OF RESECTION FOR TUBERCULOSIS AS REPORTED FROM VARIOUS CLINICS

Author	Number of Cases or Resections*	Inclusive Dates of Resections	Type of Resection				Results in Per Cent†			
			Pneumonectomy	Lobectomy	Segmental Resection	Wedge Resection	Well and Arrested	Dead	Active Disease‡	Status Unknown
Bailey *et al.* (40)	200	1947–1949	120	65	15	—	66.0	26.5	3.0	4.5
Bickford *et al.* (2)	223	–1950	100	105	18	—	88.3	4.0	4.9	0.5
Chamberlain *et al.* (4)	300*	1948–1952	—	—	265	35	93.7	3.0	3.3	—
Davidson *et al.* (41)	487	1944–1952	333	150	29	—	61.2	19.9	6.8	12.1
Day *et al.* (14)	202	1945–1949	104	98	—	—	74.3	12.4	13.4	—
Forsee (5)	443	1947–1952	22	261	65	95	91.0	9.0	3.2	0.7
Kelley and Pecora (6)	107	1948–1951	36	45	26		87.7	2.8	6.1	6.1
Murphy *et al.* (42)	100	1945–1948	51	49	—	—	81.0	9.0	10.0	—
Overholt *et al.* (16)	200*	1934–1946	127	73	—	—	45.5	23.0	20.0	11.5
Overholt *et al.* (7)	437*	1934–1950	289	119	29	—	70.9	20.4	8.1	0.5
Sweet (18)	63	1943–1945	36	27	—	—	41.3	44.4	14.3	—
This report	226	1949–1953	37	78	65	46	80.5	3.1	6.6	9.7

* Resections.

† The period of follow-up varied greatly.

‡ Includes respiratory cripples in a few instances.

TABLE 12

COMPLICATIONS OF RESECTION AS REPORTED FROM VARIOUS CLINICS

Author	Number of Cases or Resections*	Inclusive Dates of Resections	Type of Resection				Drug Therapy		Complications in Per Cent‡§				
			Pneumonectomy	Lobectomy	Segmental Resection	Wedge Resection	Yes†	No	Spread or Exacerbation	Bronchopleural Fistula	Lung Leak	Empyema	Bronchial Stump Ulcer
Bailey *et al.* (40)	200	1943–1949	120	65	15	—	100		1.0	4.0	—	3.0	—
								100	13.0	14.0	—	13.0	—
Bickford *et al.* (2)	729*	–1952	178	292	259	—	?		4.3	2.2	—	3.4	—
Brewer *et al.* (3)	121*	1945–1954	—	—	121		121	—	3.3	1.7	—	1.7	—
Chamberlain *et al.* (4)	300*	1948–1952	—	—	265	35	300	—	3.0	5.3	—	4.3	—
Davidson *et al.* (41)	512*	1944–1952	333	150	29	—	?		5.9	16.2	—	2.3	—
Day *et al.* (14)	202	1945–1949	104	98	—	—	?		12.4	13.4	—	13.4	—
Forsee (5)	443	1947–1952	22	261	65	95	428	15	1.8	2.5	—	2.5	—
Kelley and Pecora (6)	107	1948–1951	36	45	26		107		5.6	7.5	—	1.9	3.7
Murphy *et al.* (42)	100	1945–1948	51	49	—	—	100		18.0	10.0	—	3.0	2.0
Overholt *et al.* (16)	200*	1934–1946	127	73	—	—	—	200	16.5	6.5	—	11.5	—
Overholt *et al.* (7)	437*	1934–1950	289	119	29	—	208		7.0	2.9	—	5.3	5.8
								229	23.1	10.0	—	13.1	12.2
Sweet (18)	63	1943–1945	36	27	—	—		63	36.5	1.6	—	9.5	—
Veterans Administration (11)	1,473*	1951–	159	608	706		1323	150	2.7	5.2	—	3.1	0.5
This report	226	1949–1953	37	78	65	46	180	46	7.5	7.5	8.8	5.3	1.8

* Resections.

† The duration of drug therapy varied greatly.

‡ The follow-up varied considerably.

§ Some authors did not report the number of cases with each complication.

Lobectomy: Few patients in the upper lobectomy group who had had a previous thoracoplasty developed lung leaks or bronchopleural fistula following resection, presumably because of preliminary "tailoring" of the bony hemithorax. There is a suggestion that pneumoperitoneum lessened the incidence of lung leaks and bronchopleural fistula following resection (table 8).

Tuberculous bronchitis: The presence of old bronchitis, not active at the time of resection in most instances, was not associated with a higher incidence of bronchopleural fistula (table 9).

Follow-up and the influence of postoperative chemotherapy: In table 10*A* the lapse of time is shown since the date of resection and in table 10*B* the results of follow-up are presented. Late tuberculous exacerbation refers to those which occurred more than twelve months following resection.

It is clear that late tuberculous exacerbations were much more common in patients who had not received adequate postoperative drug therapy (figure 4). Almost ten times as many *Group 1* patients, who did not receive adequate postoperative drug therapy, developed late tuberculous exacerbations as did the patients in *Group 2*, who received adequate postoperative drug therapy.

Results of resection: In table 11 the past and improved present results of re-

section for tuberculosis are recorded. The over-all results correspond closely to those reported for similar groups of cases in other clinics.

Complications of resection: The complications of resection during the past several years, showing the progressive decrease in the incidence of the specifically tuberculous complications, are shown in table 12. The present experience is little different from that reported by others for similar groups of cases. Nontuberculous complications now constitute the greatest bulk of the complications following pulmonary resections for tuberculosis.

DISCUSSION

Forsee (5) wisely observed that antimicrobial therapy was the "common denominator" of success in resection for tuberculosis. The influence of antimicrobial therapy is far reaching. In conjunction with rest and sometimes pneumoperitoneum, chemotherapy brings about the maximum improvement of the disease which is possible. Cavities frequently close, marked regression of disease occurs, stable disease is the rule, bronchial disease heals, and the sputum usually becomes negative for tubercle bacilli on culture even though an open cavity may exist. The enormous effectiveness of these measures is reflected in the appreciably fewer numbers of patients with extensive and flagrant disease who must be considered for resection. Moreover, the marked resolution of disease following antimicrobial therapy allows the use of more limited types of resection, and many fewer pneumonectomies are required.

At least three or four months of chemotherapy are essential in the preoperative period, and often longer periods are necessary. It would be a mistake to credit the advances in surgical technique and related factors to more than a modest degree for the lowering of tuberculous complications. The credit is largely due to the effects of drug therapy, a lesson which was learned by experience (13–18).

The influence of long-term antimicrobial therapy on the control of residual tuberculous disease has been striking. This is reflected in the more favorable course following pulmonary resection, for the majority of such patients have residual tuberculous disease. The drug therapy should be continued for at least four to twelve months after the inactivity of the residual disease has been determined.

The timing of the resection in relation to the course of the pulmonary tuberculosis is of the greatest importance. One of the real advantages of the use of resection is to shorten the period of treatment and disability. At least three or four months of chemotherapy is essential to ensure the safety of a resection. Obviously, a longer period may be necessary in more extensive disease and when there is regressing contralateral disease. If the lesion is well localized, of long standing, and of relatively low-grade or questionable activity, the period of chemotherapy may be shorter. In the latter instance, the sputum should be negative for tubercle bacilli on culture. There is no reason, however, to delay resection for many months in order to attain the greatest improvement of disease which might eventually be possible. Resection is appropriately timed when a very substantial improvement of the disease has been brought about,

even though it may still be improving slightly; when contralateral disease is absent or is of proved stability; and preferably when the sputum is noninfectious. Resection can safely be done approximately four to six months after starting drug therapy under these circumstances. It is well known that cavities do not often close after six or eight months of chemotherapy (19, 20). To postpone resection for several months after such a period is unnecessary, provided other considerations allow resection. Indeed, such a policy may be dangerous, for tubercle bacilli might appear in the sputum and the infection might become drug resistant. It is as true today as it ever was that resection is less safe if the sputum is infectious and drug-resistant tubercle bacilli are present (11, 20–22). On the other hand, in the experience of the present writers, resection of cavitary lesions, provided associated exudative lesions are reasonably stable, sufficient drug therapy has been given, and the sputum is noninfectious, is little or no more hazardous than the resection of other lesions. Forsee (5) and Murphy (22), while not making all of the above distinctions, have not found this to be so. Many patients with uncontrolled cavernous disease have previously had drug therapy; their response to re-treatment with drugs is usually not satisfactory and the sputum remains positive for tubercle bacilli (11, 20, 22).

Bronchopleural fistula and related empyema and lung leaks or small bronchopleural fistula are the chief complications of resection today. Segmental resection is associated with a considerable incidence of lung leaks and other minor complications in the experience of many surgeons (9, 12, 23–26). This has certainly been the experience in the present study. The resection of a segment from a lobe which has been extensively diseased at some time previously is particularly hazardous (3, 4, 25). The intersegmental plane is often partially obliterated, making separation of the segment most difficult and unsatisfactory, and air leaks from the lung tissue, which is usually emphysematous, are numerous and difficult to control. If resection is definitely indicated, lobectomy is a safer operation in these circumstances. If resection is not definitely indicated, thoracoplasty may be a wise substitute for resection. This belief is shared by others (3–5, 25).

At the time of resection, if it appears that the remaining lung cannot or probably will not fill the pleural space, it is wise to perform a simultaneous thoracoplasty. The writers' experience suggests that pneumoperitoneum may be helpful in effecting prompt obliteration of the pleural space following resection, particularly in resection of the lower lobe or segments of the lower lobe. Brewer and associates (3) have made similar observations in using thoracoplasty and pneumoperitoneum with resection.

It was pointed out above that right pneumonectomy is questionably more hazardous than left pneumonectomy, and it was suggested that this might be related to the more frequent presence of a thoracoplasty prior to left pneumonectomy. The overdistension of the contralateral lung might be minimized with a thoracoplasty prior to pneumonectomy; and consequently the tendency for contralateral disease to exacerbate could be minimized. With the use of chemotherapy for a number of months preoperatively, the writers have seen few contralateral lesions worsen following pneumonectomy; therefore, they have not

adopted the practice of performing a thoracoplasty routinely prior to pneumonectomy. It is believed that a "tailoring" thoracoplasty following pneumonectomy may be of considerable benefit, particularly if the contralateral lung becomes overdistended or contralateral disease is present and is more than minimal in extent.

The place of resection in the management of the small residual pulmonary lesion is clearly a controversial subject (8, 27, 28). The effectiveness of long-term drug therapy in the control of residual inactive pulmonary lesions, "nodular" lesions, "closed" lesions, or "target-point" lesions has been impressive (1, 20, 29). Judging from past experience with tuberculosis (20, 30, 31, 43), and on the basis of pathologic and bacteriologic findings (8, 26, 32–37), there is some reason to believe that resection of significant residual lesions will improve the eventual course of the disease (4, 8, 38). The proof will come with the careful follow-up of patients with comparable disease who have and have not had resection as a part of their treatment.

The selection of patients who need resection of residual lesions is difficult at times. Surely not all residual lesions can be excised (27), but the more significant and hazardous lesions can. Admittedly, it is not possible to tell with a satisfactory degree of certainty which lesions are potentially hazardous and which lesions are benign, at least for the present. There are, however, some good leads.

One would think that all residual lesions following apparently satisfactory therapy are the same. Everyone knows that they are not and that their similarity often stops with some arbitrary definition of the lesion, such as the triad of cavity closure, stable roentgenographic findings, and reversal of infectiousness. Lesions meeting these criteria may nevertheless have a widely different pathogenesis and course. Some such lesions might have originally represented one or more cavities which had become inspissated, and others might represent small nodular caseous lesions which remained following the resorption of small exudative lesions. Although statistical proof is lacking, clinical experience suggests that inspissated cavities and probably the large residual caseous nodules do not have so favorable an outlook as the small nodular lesions which remain following the resorption of exudative lesions. Cavities which appear closed at the time of roentgenographic examination are often found to be very tenuously closed when resected, and almost all "closed" cavities have a significant bronchial communication. The larger a necrotic nodule is, the more likely it is to have a significant bronchial communication. Sloughing of infected necrotic material and spread of disease probably occur more often in the presence of such bronchial communications (4, 34, 35, 38).

For the above reasons it is believed that lesions previously represented by cavities more than 2 or 3 cm. in diameter, lesions in which cavities closed slowly (during more than three or four months), and lesions in which residual nodules are more than 1 and certainly 2 cm. in diameter should be resected.

The results of bacteriologic study of resected lesions is very pertinent. It is well known that, in patients who have had long-term drug therapy preoperatively, microscopic examination of the resected closed lesion shows bacilli in 75 per cent of the lesions; however, the bacilli can be cultured in only 5 to 20 per

cent of such lesions (26, 33, 36). There is a lively controversy concerning the viability of the organisms (37). Some believe that present culture techniques are not adequate to culture the bacilli under the conditions found in the caseous lesions (32, 37), and the findings of Hobby and associates (39) lend support to this belief. Others believe that the nonculturable bacilli are surely dead (37). The answer to this problem is obviously of the greatest importance and may modify our present attitude toward the resection of these lesions. Since there is a definite incidence of relapse in patients who have had the advantage of prolonged drug therapy (20, 29), there is reason to believe that all of the bacilli are not dead.

The hazards of resection, however slight, are too great if the patient would have recovered and remained well without resection. Similarly, an increased incidence of relapse in patients with similar lesions which were suitable for, but did not have, resection is too great if resection could have safely prevented it.

SUMMARY

The results of treatment, the incidence and nature of complications, and the relationship of certain factors to the incidence and nature of complications have been presented in a group of 226 pulmonary resections. Pneumonectomy was performed in 16.4 per cent of the cases, lobectomy in 34.5 per cent, segmental resection in 28.8 per cent, and wedge resection in 20.4 per cent of the cases.

In December, 1953, 80.5 per cent of the patients had arrested disease, 6.6 per cent had active disease, 3.1 per cent were dead, and the status of 9.7 per cent was unknown. Complications, within one year of resection, occurred in 26.5 per cent of the cases. Tuberculous complications occurred in 10.2 per cent of the cases, bronchopleural fistula in 7.5 per cent, lung leaks in 8.8 per cent, and empyema in 5.3 per cent.

The enormous influence of preoperative and postoperative antimicrobial therapy on the results and complications of resection has been stressed. At least four months of chemotherapy should precede resection, and at least six to twelve months should follow, depending on the status of the residual lesions.

The influence of other factors on the incidence of complications was presented. These included the indication for operation, extent of disease, and the type of resection. They were closely inter-related, as well as being related to the effects of drug therapy.

The prognosis of a patient who has had a resection is the prognosis of residual disease. The management of such a patient should not differ from the management of other patients with similar residual disease.

SUMARIO

El Puesto de la Resección en la Asistencia de la Tuberculosis Pulmonar

Preséntanse, para un grupo de 226 casos de resección, los resultados del tratamiento, la incidencia y naturaleza de las complicaciones y la relación de ciertos factores con estas incidencia y naturaleza.

En 16.4 por ciento de los casos se ejecutó la neumonectomía, en 34.5 por ciento la lobectomía, en 28.8 por ciento la resección segmental y 20.4 por ciento la resección cuneiforme.

En diciembre de 1953, 80.5 por ciento de los enfermos tenían la dolencia estacionada, 6.6 por ciento tenían enfermedad activa, 3.1 por ciento habían fallecido y se desconocía

el resultado en 9.7 por ciento. En 26.5 por ciento de los casos, sobrevinieron complicaciones en término de un año de la resección. En 10.2 por ciento, hubo complicaciones tuberculosas, en 7.5 por ciento fístula broncopleural, en 8.8 por ciento escurrimientos pulmonares y en 5.3 por ciento empiema.

Recálcase el enorme influjo ejercido por la farmacoterapia pre- y postoperatoria sobre los resultados y las complicaciones de la resección. Esta debe ir precedida a lo menos de cuatro meses de medicación y seguida a lo menos de seis a doce meses de la misma, conforme al estado de las lesiones residuales.

Expónese el influjo de otros factores sobre la incidencia de las complicaciones, comprendiendo la indicación operatoria, la extensión de la enfermedad y la clase de resección, hallándose aquéllos entrelazados y además relacionados con los efectos de la farmacoterapia.

El pronóstico en un enfermo sometido a la resección es el pronóstico de la enfermedad residual. La asistencia del sujeto no debe discrepar de la suministrada a sujetos que tienen enfermedad residual semejante.

RESUME

La place de l'exérèse dans le traitement de la tuberculose pulmonaire

Présentation des résultats du traitement, de l'incidence et de la nature des complications et des rapports entre certains facteurs et l'incidence et la nature des complications dans un groupe de 226 cas d'exérèse.

La pneumonectomie a été pratiquée dans 16,4% des cas, la lobectomie dans 34,5%, la résection segmentaire dans 28,8%, la résection "en coin" (wedge resection) dans 20,4% des cas.

En décembre 1953, chez 80,5% des malades, la maladie était stabilisée, elle était en activité chez 6,6% d'entre eux, 3,1% des malades étaient morts, l'état de 9,7% des malades n'était pas connu. Des complications se sont produites dans 26,5% des cas pendant l'année suivant la résection. Des complications de nature tuberculeuse se sont produites dans 10,2% des cas, des fistules broncho-pleurales dans 7,5% des cas, des fistules pulmonaires dans 8,8% des cas et l'empyème dans 5,3% des cas.

L'influence considérable du traitement médicamenteux pré et postopératoire sur les résultats et les complications de l'exérèse est mise en évidence. La durée de la chimiothérapie doit être de quatre mois au minimum avant la résection au moins de six à douze mois après, selon l'état des lésions résiduelles.

L'influence d'autres facteurs sur l'incidence des complications est présentée. Ces facteurs comprennent l'indication opératoire, l'étendue de l'affection et le type de résection. Leur corrélation était très étroite et ils étaient également liés aux effets de la chimiothérapie.

Le pronostic, chez le malade soumis à la résection, est le pronostic de la lésion résiduelle. Le traitement du malade ne doit pas être différent de celui appliqué chez tout malade affecté de lésions résiduelles semblables.

Acknowledgment

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Addendum

Since this paper was submitted for publication (June, 1955), 3 additional patients with complications have come to the writers' attention. One patient, a young diabetic, developed a small air-fluid space several months following segmental resection of the superior segment of the right lower lobe. This quickly responded to aspiration, and culture of the aspirated fluid was negative for tubercle bacilli. One patient had an exacerbation of an old contralateral lesion several months following wedge resection. One patient had an exacerbation of an ipsilateral lesion in the superior segment of the right lower lobe following right upper lobectomy.

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Case Reports

OBSERVATIONS ON THE EFFECT OF CORTISONE IN THE TREATMENT OF TUBERCULOUS MENINGITIS[1]

Report of Two Cases

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Although it is generally agreed that cortisone exerts a deleterious effect on pulmonary tuberculosis, there is some evidence that it may be of value in the treatment of tuberculous meningitis. When used in conjunction with antituberculous chemotherapy, the hormone may be helpful in preventing cerebrospinal fluid block, the most dreaded complication of that disease.

Cortisone was added to the therapeutic regimen of the 2 cases of tuberculous meningitis reported herein. The extreme results of such treatment are represented. One of these cases is particularly noteworthy in that tuberculous subdural effusion was noted, a complication of this disease which has rarely been reported.

CASE REPORTS

Case 1. E. W., a 2-year-old Negro female, was admitted to Dooley Hospital on March 13, 1954, with history of fever, vomiting, and listlessness of five days' duration. She had been well until three weeks prior to admission, when thick yellow drainage appeared in the left ear canal, with no history of previous symptoms referable to the ear. Two weeks before admission a cough and congested nose were observed as well as "redness of the eyes." Shortly afterward a rash appeared on her face and spread to the extremities and trunk. Although she was not seen by a physician, this was assumed to be measles. The rash persisted for approximately one week. About one week before admission she seemed to have improved but shortly thereafter became lethargic and febrile. Anorexia, vomiting, and restlessness were noted and she was referred to Dooley Hospital with the tentative diagnosis of meningitis.

There was no family history of tuberculosis and no history of contact with tuberculosis.

Physical examination at the time of admission revealed the patient to be acutely ill. She was lethargic, the skin was hot and dry, and turgor was somewhat impaired. The fontanelles were closed, but there was some nuchal rigidity. The left external auditory canal was filled with inspissated sanguino-purulent exudate. There was conjunctival injection of the left eye with yellow purulent exudate. The tonsils and posterior pharynx were mildly injected and enlarged, tender, posterior cervical and auricular lymph nodes were observed. There was a large reducible umbilical hernia. The deep tendon reflexes were hypoactive. Brudzinski and Babinski signs were absent and Kernig's sign was questionable.

A chest roentgenogram revealed some hilar and midtrunk mottling, suggesting a mild bronchial infection. Later chest roentgenograms showed prominence of the left hilus compatible with primary pulmonary tuberculosis. A tuberculin test (0.001 mg.) was positive. Cerebrospinal examination showed 153 leukocytes; protein, 200 mg. per 100 ml.; sugar, 28 mg. per 100 ml.; and chlorides, 102 mEq. per liter. Cerebrospinal fluid culture subse-

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quently revealed the presence of acid-fast organisms. Blood electrolytes were essentially normal. A serologic test (Wasserman) was positive in dilution 1:32 and a cerebrospinal fluid test (Wasserman) was positive to the second dilution. A serologic test for syphilis (blood) was negative on September 30, 1954.

On admission, therapy consisted of penicillin, streptomycin, chlortetracycline ophthalmic ointment, and parenteral fluids. When the tuberculin test was found to be positive, isoniazid and para-aminosalicylic acid (PAS) were added to the regimen. Isoniazid, PAS, streptomycin, and penicillin were continued until a few weeks before discharge from the hospital.

On the day following admission, the patient had several generalized convulsive seizures which were difficult to control. At that time, cerebrospinal fluid examination showed the presence of 404 leukocytes with 66 per cent lymphocytes; protein, 180 mg. per 100 ml.; sugar, 70 mg. per 100 ml.; and chlorides, 102 mEq. per liter. She was comatose for twenty-four hours following the seizures, gradually began to respond slowly, and nine days later was able to take fluids and diet fairly well without assistance. There was residual paresis of the left arm and left leg.

When subsequent lumbar punctures were performed the cerebrospinal fluid flowed slowly and, finally, on April 16, 1954, one month after admission, only a small amount of intensely yellow fluid could be obtained. Examination of the fluid at this time showed 2,250 leukocytes with 95 per cent lymphocytes, and protein 5,600 mg. per 100 ml. (figure 1). Cerebrospinal fluid block appeared certain and cortisone, 100 mg. daily, was given for two weeks, then gradually decreased, and finally discontinued after one month. After slightly more than two weeks of cortisone therapy (May 4, 1954), the cerebrospinal fluid protein was 650 mg. per 100 ml., but it rose rapidly as cortisone dosage was decreased. On May 11, 1954, cerebrospinal fluid protein content was 1,500 mg. per 100 ml. and after another week was 3,900 mg. per 100 ml. with 21 leukocytes present at that time. Two weeks later (June 1) cerebrospinal fluid protein content had risen to 5,800 mg. per 100 ml.

Cortisone therapy was reinstituted on June 6, 1954, (two and one half months after admission) and the patient was given a dosage of 300 mg. daily for two days, 200 mg. daily for four days, and 100 mg. daily for the ensuing six weeks.

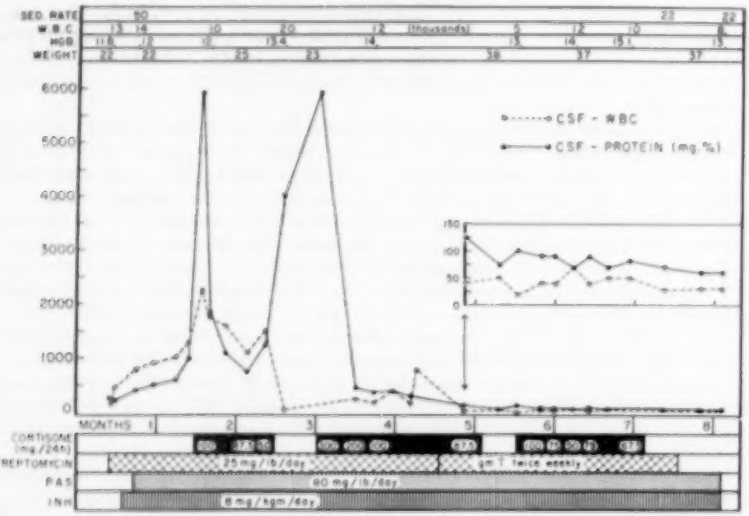

FIG. 1. Diagram depicting precipitous fall of cerebrospinal fluid protein when cortisone therapy was instituted.

At the end of this time cerebrospinal fluid protein content was 95 mg. per 100 ml. Cortisone was thereupon gradually decreased over the ensuing two-week period and, at the time of discontinuation (August 9, 1954), cerebrospinal fluid protein content had risen to 150 mg. per 100 ml. and a third course of cortisone therapy was begun. The drug was administered in a dosage of 100 mg. daily for two weeks and the cerebrospinal fluid protein content fell to 70 mg. per 100 ml. Cortisone dosage was gradually reduced and finally discontinued after approximately two months (October 11, 1954). At the time of discontinuation of therapy, cerebrospinal fluid examination revealed 21 lymphocytes and protein 70 mg. per 100 ml.

With each course of cortisone therapy, the patient developed a Cushing syndrome. With the final course she gained a great deal of weight and developed a moon facies. With the second course, euphoria was present in addition to these features. When the second course was discontinued, she became depressed and cried easily. At the conclusion of the third course, however, she was given corticotropin,[2] 80 mg. daily for three days, and the withdrawal symptoms did not appear.

Physical therapy was instituted on April 27, 1954, six weeks after admission. The patient improved rapidly and by August 4, 1954 (almost five months after admission) there was no sign of hemiparesis and the patient had good strength in all muscles. She was discharged on October 11, 1954, in good condition and apparently well except for the residual signs of the Cushing syndrome.

Case 2. R. M., a 16-month-old Negro male, was admitted to Dooley Hospital on August 18, 1954, with a history of having been "very sleepy" for two days. He was well until three months before admission when he contracted an 'itching rash," which first appeared on the scalp and behind the ears and then spread over the trunk. He was treated by the family doctor, and the rash subsided. One month before hospitalization he had a convulsion which lasted for two minutes. Two days before admission to Dooley Hospital the patient was taken to Mary Washington Hospital, Fredericksburg, Virginia, with a history of vomiting during the preceding week, excessive sweating for three days, and yellow, foamy stools for two days. He was treated with a sulfonamide and tetracycline and referred to Dooley Hospital.

There was no family history of tuberculosis and no history of contact with tuberculosis.

On admission, physical examination revealed an acutely ill, flaccid, comatose infant, who was well developed, well nourished, and moderately dehydrated. Painful stimuli produced no response. Breathing was Cheyne-Stokes in character. Temperature was 98°F., pulse 150 per minute, and respirations were 22 per minute. The anterior fontanelle was patent 3 cm. and bulged slightly with some pulsation. The left pupil was larger than the right. Fundoscopic examination was normal. The right side of the mouth appeared to droop. There was slight nuchal rigidity, and deep tendon reflexes were hyperactive. Babinski, Kernig, and Brudzinski signs were absent, and there was no clonus.

A chest roentgenogram showed an area of increased density involving the upper third of the left lung (figure 2). Intradermal tuberculin test (0.1 mg.) was positive. Cerebrospinal fluid examination revealed 277 leukocytes with 98 per cent lymphocytes. Cerebrospinal fluid protein content was 240 mg. per 100 ml., sugar was 43 mg. per 100 ml., and chlorides were 102 mEq. per liter. Culture of the fluid subsequently revealed the presence of acid-fast bacilli.

At the time of admission, tubal feedings were instituted and therapy was begun. This included isoniazid, streptomycin, PAS, multiple vitamins, and iron. This was continued throughout his hospital stay and penicillin and tetracycline were also added. Blood transfusions were given at indicated intervals.

Eight days following admission there was little change in the patient's condition. He was still comatose, flaccid, and appeared moribund. Painful stimuli produced practically no response. At that time cortisone, 200 mg. daily, was added to the regimen. Approximately two weeks later the patient appeared to show slight improvement, with more active response to painful stimuli. He developed decerebrate rigidity, however, and remained in this state

[2] In the form of Acthar Gel®, product of The Armour Laboratories.

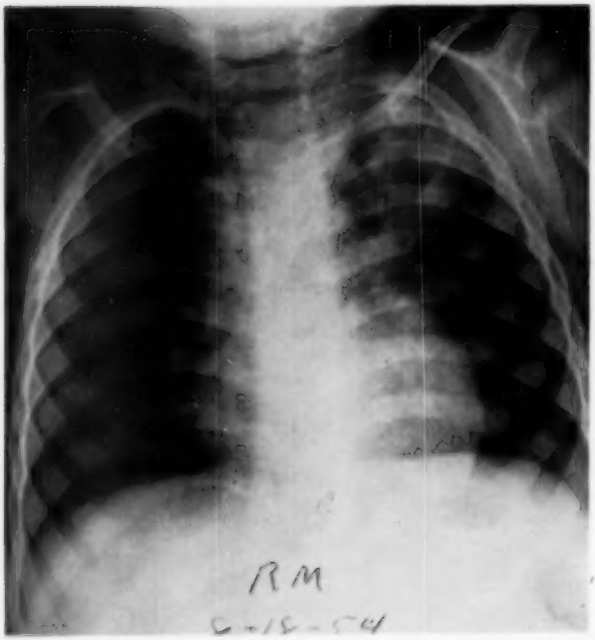

FIG. 2. *Case 2* (R. M.). Admission chest roentgenogram, showing area of infiltration in upper third of left lung.

until his death. Decubitus ulcers appeared on the scalp and buttocks and the body temperature was very labile, often being elevated to 105° and 108°F. Cheyne-Stokes respirations persisted.

Six weeks after admission, a chest roentgenogram revealed an area of decreased density, 3 cm. in diameter, in the left upper lung. This was later shown to be a cavity and it had increased in size to 5 cm. at the time of the patient's death (figure 3).

Four months after admission (December 16, 1954) it was noted that the head circumference was 51 cm., an increase of 2 cm. in a five-week period. Subdural tap two days previously had been productive of 30 ml. of clear, slightly yellow fluid on the right. Paracentesis of the left subdural space produced no fluid. The subdural fluid showed one polymorphonuclear cell; protein, 20 mg. per 100 ml.; sugar, 240 mg. per 100 ml.; and chlorides, 165 mEq. per liter. On the day following demonstration of the subdural effusion, the patient developed oliguria. This progressed to anuria and he died twenty-four hours later. Cerebrospinal fluid examination three days before death showed 12 lymphocytes and protein 30 mg. per 100 ml. (table 1).

Blood chemistries on the final day of life were as follows: sodium, 145 mEq. per liter; chlorides, 118 mEq. per liter; potassium, 6.7 mEq. per liter; carbon dioxide combining power, 5 mEq. per liter; blood urea nitrogen, 135 mg. per 100 ml.; and blood sugar, 340 mg. per 100 ml.

Autopsy findings: (R. M. (A-8321)): The body was that of a well-developed, well-nourished, Negro male infant with moderate cyanosis. The anterior fontanelle was widely open and slightly bulging. The left pleural cavity contained approximately 100 ml. of light yellow fluid and showed apical fibrous adhesions. The upper lobe of the left lung was almost

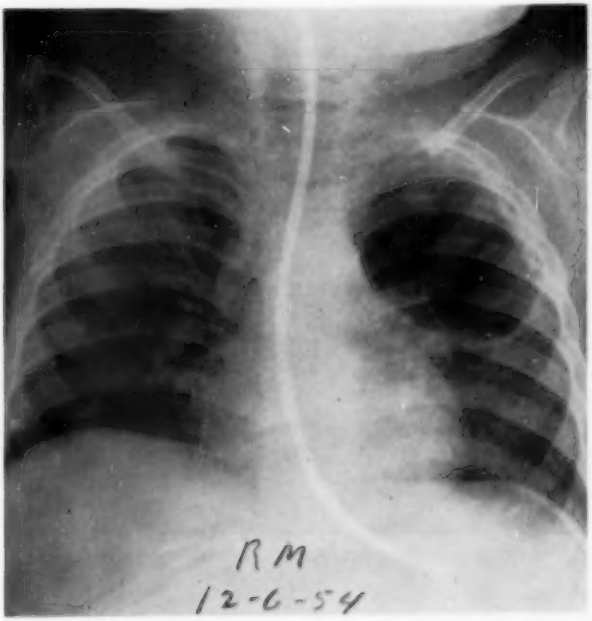

FIG. 3. *Case 2* (R. M.). Later roentgenogram showing cavity 5 cm. in diameter

entirely replaced by a large cystic cavity measuring 5 cm. in diameter. There was a small amount of caseous flaky material covering a gray smooth lining of the cavity, which was traversed by trabeculae.

The cavity wall was thin and fused with the visceral pleura in the apical portion (figure 4). Microscopically, the cavity wall, consisting of concentric fibers of fibrous connective tissue, was quite vascular and contained a small amount of infiltrate which was chiefly lymphocytic. A few epithelioid cells and Langhans' giant cells were present, but no distinct tubercle formation could be found in the cavity wall or in the immediately adjacent pulmonary tissue (figure 5). A few small bronchi and bronchioles were imbedded in the fibrous

TABLE 1

CEREBROSPINAL PROTEIN AND LEUKOCYTE VALUES IN CASE 2 (R. M.)
(Cortisone, 200 Mg. to 12.5 Mg. Daily: Begun on August 26, 1954; Discontinued on November 26, 1954)

Month	8	8	8	8	9	9	9	10	10	10	11	11	11	12	12
Day	18	23	25	30	7	13	27	4	11	25	2	10	29	6	13
Leukocytes	277	642	424	121	12	28	9	12	26	8	27	6	8	14	12
Protein (mg. per 100 ml.)	240	220	87	130	128	240	45	75	90	135	45	60	60	40	30

FIG. 4. The thin-walled cystic cavity of the lung with trabecular and caseous debris on the wall.

FIG. 5. Histologic appearance of the cavity wall. There is sparcity of inflammatory cells in the wall. One giant cell and a few epithelioid cells are visible. The caseous necrosis and calcific deposition may be seen.

connective tissue of the cavity wall. The inner surface of the cavity was lined by caseous material with fine calcium deposits. A few small foci of tuberculous granulation tissue were found at the junction between the caseous content and the fibrous wall of the cavity. No tuberculous lesions were found in the remainder of the lungs other than the cavity.

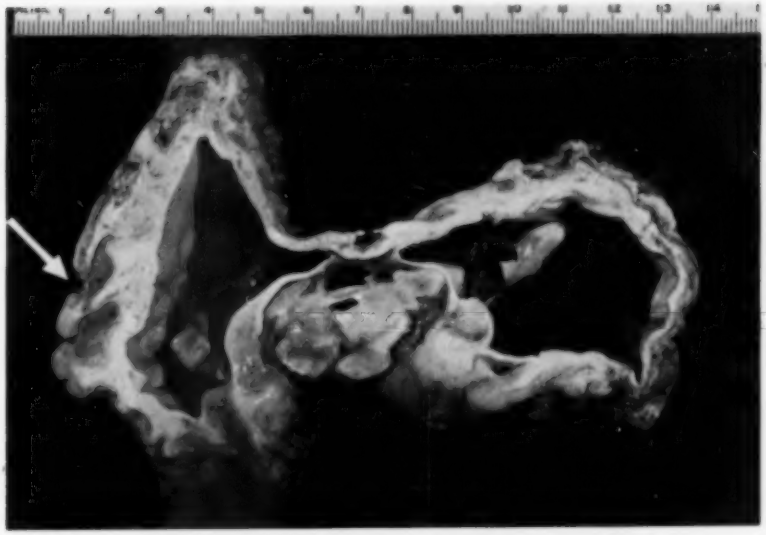

FIG. 6. A coronal section of the brain showing marked hydrocephalus, softening of the brain substance, and thrombosis of a meningeal vessel, indicated by an arrow.

The bronchial lymph nodes showed extensive caseous necrosis with small numbers of epithelioid cells, Langhans' giant cells, and lymphocytes, and a moderate degree of fibrosis at the periphery. The bronchial lymph nodes which were not involved in the caseous process, mediastinal lymph nodes, and mesenteric lymph nodes showed the presence of multiple, small, nodular areas of hyaline scarring suggestive of healed granuloma.

Ziehl-Neelsen stain revealed no acid-fast organisms in the cavity or in the bronchial lymph nodes.

When the cranial cavity was entered, approximately 40 ml. of clear fluid escaped from the subdural spaces. The brain showed marked symmetrical internal hydrocephalus with severe atrophy of the brain substance (figure 6). The leptomeninges at the base of the brain were gray and opaque (figure 7). The meningeal vessels were often found to be occluded with thrombi, and there were wide-spread infarcts throughout the brain, brain stem, and cerebellum. One microscopic caseous tuberculoma was found in the hypothalamus. It was located immediately below the ependymal lining of the third ventricle. Microscopically, the leptomeninges appeared edematous and contained a few lymphocytes in some areas and showed dense fibrosis in other places. The thrombi of the brain substance varied in age from recent liquefaction necrosis to replacement by gliosis. No obliterating vasculitis was found in the meninges. A tiny tubercle without caseous necrosis was found in the root of the tenth cranial nerve.

Other findings of interest included acute diffuse, nonhemorrhagic pancreatitis and microscopic renal vein thrombosis.

Anatomical diagnosis:

Tuberculous cavity of left upper lobe of lung
Caseous lymphadenitis of bronchial lymph nodes
Chronic tuberculous meningitis with marked internal hydrocephalus
Tuberculoma of hypothalamus (microscopic)
Subdural effusion

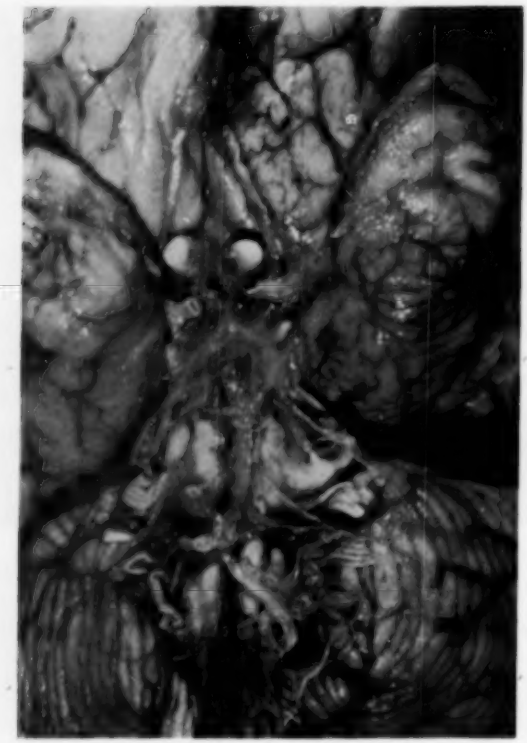

FIG. 7. Opacity of meninges in the interpeduncular fossa

Thrombosis of meningeal vessels
Infarcts, multiple, of cerebrum, brain stem, and cerebellum
Acute diffuse nonhemorrhagic pancreatitis
Renal vein thrombosis (microscopic)
Acute mucosal (superficial) ulcer of stomach

COMMENT

Apparently, cortisone acts to suppress the usual inflammatory response of the body with impairment of granulation tissue formation, macrophage activity, and fibroblastic repair (1). From the nature of this mechanism, it appears likely that cortisone promotes progression of tuberculous disease in the lung. On the other hand, when used in conjunction with antituberculous agents, it is logical to assume that the drug may be helpful in the treatment of tuberculous meningitis (2). In this form of tuberculosis failure in treatment is not primarily due to inability of the antituberculous drugs to overcome the organisms, but rather to the early development of a fibrinous exudate which is often the causative process in cerebrospinal fluid block (3). This brief statement of action may be oversimplified. There appears to be some difference of opinion whether or not the deleterious effect of the steroid can be minimized and the favorable effect magnified when antituberculous drugs are used in conjunction with cortisone.

Case 2 demonstrates a failure of cortisone with respect to the meningitis. Moreover, the pulmonary lesion progressed to cavity formation during the antimicrobial and hormone therapy. Under ordinary conditions, cortisone would not have been used when a pulmonary lesion was known to exist. The patient was moribund, however, and there appeared little to lose. Actually, he showed temporary improvement following institution of cortisone therapy, but the course ultimately led to a fatal outcome. It is noteworthy that no sign of active tuberculous disease could be noted in the lungs at autopsy. Although determination of protein and leukocytes in the cerebrospinal fluid varied widely, values which were essentially normal existed after a little more than two months of cortisone therapy. Examination three days before lethal exodus showed 12 lymphocytes and protein content of 30 mg. per 100 ml. The tuberculous meningitis appeared to be controlled.

Large cystic cavities of tuberculous origin are apparently rare in infancy and childhood. A review of the English literature in recent years makes no reference to the development of large tuberculous cavities in first infection in the age group of the patient presented here. Experimentally, it has been found that, no matter how small a dosage of fully virulent bacilli was used, a progressive pulmonary lesion developed wherever tubercle bacilli happened to lodge in the lungs. Although cavitary disease could be produced, if an animal survived for a long period of time, a pattern similar to that observed in reinfected animals could not be consistently produced (9). Pinner (10) refers to excavation appearing in the parenchymal focus of first infection tuberculosis (Ghon lesion).

In the case presented here (*Case 2*), the problem arose whether the cavity represented a true tuberculous lesion or was a congenital cyst invaded by tuberculous granulation tissue. The presence of a paper-thin cyst wall suggested a nontuberculous origin but it is now recognized that tuberculous cavities may show this type of healing under the influence of antimicrobial therapy (11, 12, 13). Moreover, the reaction throughout the entire wall of the cyst was of the tuberculous type. In the immediate vicinity of the cyst no tuberculous lesions were seen, as might be expected if the cavity was of nontuberculous origin and secondarily invaded by tubercle bacilli.

The occurrence of subdural effusion is noteworthy. The mechanism involved is probably not different from that which exists in subdural effusion which occurs in other types of bacterial meningitis. However, tuberculous subdural effusion has rarely been reported. The yellow fluid is similar to that previously described by other workers (14–18), but the normal protein content raises a question. Presence of an excess amount of fluid in the subdural space at autopsy corroborates the validity of the observation. A logical explanation of the normal protein content of the fluid is furnished by *Case 1*. In the patient of this case, the extremely high protein content of the cerebrospinal fluid returned to normal under cortisone therapy. It seems likely that the high protein content of the subdural effusion noted in *Case 2* was also reduced by treatment with cortisone.

The presence of internal hydrocephalus in *Case 2* lends credence to the observation (19) that internal hydrocephalus occurs early in the course of tuberculous meningitis and is often reversible. Perhaps it may also be assumed that the use of cortisone may often cause cerebrospinal fluid block to be reversible. Certainly the patient of *Case 1* showed every clinical sign of cerebrospinal fluid obstruction, and on cortisone therapy the evidences of "block" disappeared.

In the autopsy of *Case 2*, examination of the meninges showed a histologic picture entirely different from untreated cases. For example, only one tubercle could be found, and this was found in the root of the vagus nerve. No caseation was present in the tubercle. Macrophage and lymphocytic response was scant and only one giant cell was observed.

No tuberculous tissue was seen in the fibrinous exudate at the base of the brain. The choroid plexi were void of involvement.

Finally, it must be pointed out that cortisone therapy increases the hazard of secondary infection with pyogenic organisms (20). Concomitant use of an antibacterial agent such as penicillin would seem mandatory in all cases.

SUMMARY

Two cases illustrating the effect of cortisone on tuberculous meningitis are reported. In one instance, apparent cerebrospinal fluid block disappeared. In the other, the protein and cellular content of the cerebrospinal fluid was reduced to normal values, but excavation of a large area of pulmonary infiltration occurred.

It appears that cortisone may be of value in the prevention of cerebrospinal fluid block associated with tuberculous meningitis. Extreme caution is indicated, however, whenever pulmonary tuberculous disease is known to exist.

SUMARIO

Observaciones sobre el Efecto de la Cortisona en el Tratamiento de la Meningitis Tuberculosa

Preséntanse 2 casos que muestran el efecto de la cortisona sobre la meningitis tuberculosa. En uno, se disolvió un bloqueo aparente del líquido céfalorraquídeo. En el otro, se redujeron a valores normales la proteína y el contenido celular del líquido, pero apareció tuberculosis pulmonar evolutiva con una gran cavidad de paredes delgadas.

La cortisona puede resultar de valor en la prevención del bloqueo del líquido céfalorraquídeo asociado con meningitis tuberculosa. Sin embargo, está indicado el ejercicio de suma cautela siempre que se conoce la existencia de enfermedad tuberculosa del pulmón.

RESUME

Observations sur l'effet de la cortisone dans le traitement de la méningite tuberculeuse

Deux cas illustrant l'effet de la cortisone sur la méningite tuberculeuse sont rapportés. Dans un cas le blocage apparent du liquide céphalo-rachidien a été dissous. Dans l'autre, la teneur en protéine et en cellules du liquide céphalo-rachidien a été ramenée à sa valeur normale, mais il s'est produit une tuberculose pulmonaire évolutive avec large caverne à paroi mince.

Il semble que la cortisone puisse se montrer utile dans la prévention du blocage du liquide céphalo-rachidien associé à la méningite tuberculeuse. Une extrême prudence est cependant indiquée en présence d'une tuberculose pulmonaire reconnue.

Addendum

Since this paper was prepared, cortisone has been used as an adjunct in the treatment of two more cases of tuberculous meningitis, uncomplicated by a demonstrable pulmonary lesion. Both patients show satisfactory progress to date.

Acknowledgment

The writers would like to express their appreciation to Dr. G. R. Hennigar for his assistance in the preparation of the pathology, and to Mr. M. C. Shaffer, Department of Visual Education, for the illustrations.

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UREMIA DUE TO URINARY SYSTEM TUBERCULOSIS[1]

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INTRODUCTION

Tuberculous involvement of the urinary system is a frequent and significant event which is well recognized clinically and pathologically. It is therefore surprising that the relevant textbooks do not mention the possibility that uremia may result from tuberculosis of the urinary tract (1). A review of the literature of the past ten years discloses no cases classified in this manner. However, two recent reviews dealing with urogenital tuberculosis casually note the frequency of this entity, thereby emphasizing the lack of attention which this subject has received.

In his summary of 208 cases of renal tuberculosis, Rosendal (2) noted that 24 patients died from uremia. Greenberger and Greenberger (3) reviewed 209 surgically treated cases of urogenital tuberculosis. Uremia caused death in 13 patients (27.7 per cent) in whom a nephrectomy had been performed. In 4 of these, the disease was bilateral at the time of operation; the other 9 patients developed contralateral tuberculosis nine months to ten years after nephrectomy. Uremia was the cause of death in 9 of 69 patients (12.3 per cent) who died following epididymectomy. Uremia also occurred in 6 patients who were subjected to both operations. In addition, uremia due to amyloidosis caused death in 4 post-nephrectomy and 5 post-epididymectomy cases.

Four cases of uremia due to tuberculosis of the urinary tract occurred among 8,154 consecutive autopsies performed at Queens General Hospital, a large general municipal hospital, from 1935 to 1949, inclusive. These 4 cases are summarized below and form the basis of the present report. Other cases may have been overlooked because no recent blood chemistries were performed or because the uremic symptoms were overshadowed by the infectious aspect of the disease.

CASE REPORTS

Case 1. J. S., a 70-year-old white male, entered the hospital because of progressively increasing urinary frequency, dysuria, and nocturia for ten months. There had been suprapubic discomfort, a 30 pound weight loss, and marked weakness.

Physical examination showed the prostate to be 3-plus enlarged with a nodular left lobe. There was moderate bladder distension. The blood pressure was 118 systolic, 70 diastolic in mm. of mercury. The urine showed 6 to 15 erythrocytes and 2 to 4 leukocytes per high-power field, with 3-plus albumin and a specific gravity of 1.012. The blood urea nitrogen progressively increased from 67 to 110 mg. per 100 ml. and the creatinine to 4.6 mg. per 100 ml. The chest roentgenogram showed a miliary type of infiltration. Intravenous urograms showed moderate bilateral hydronephrosis and hydroureter. The bladder contained 300 ml. of residual urine. The patient was placed on tidal drainage. He showed a low-grade intermittent fever, and died on the ninth hospital day. The final clinical diagnosis was carcinoma of the prostate with bilateral hydronephrosis and hydroureter, possible silicosis.

Post-mortem examination: At post-mortem examination, the right kidney weighed 280 gm. and the left, 340 gm. Both kidneys were surrounded by indurated tissue. The capsules stripped with some difficulty, leaving a finely granular cortical surface. The cortices were normal in width and well differentiated from the medulla. The left kidney showed several

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gray-white streaked areas radiating up the medullary pyramids to involve the inner zone of the cortex. Both pelves were markedly thickened, with replacement of the entire mucosa by a shaggy yellow-white exudate except for the lower calyx on the right. Both ureters were similarly involved, the left more than the right. The left ureter was represented by a stiff, thickened tube. Both ureteral orifices were easily probed. Overhanging the right ureteral orifice, a small papillomatous mass, 0.5 cm. in diameter, projected from the bladder mucosa. The bladder mucosa was covered by a thick mucopurulent exudate with ulceration in the region of the left ureteral orifice. The prostate contained several nodular caseous tuberculomas. The seminal vesicles were indurated with opaque gray-white foci. The lungs contained numerous miliary areas of tuberculosis. In addition, a tuberculous ulcer of the ileum and a caseous tuberculoma of the left adrenal were observed.

Microscopic examination: Microscopic examination confirmed the gross findings and showed multiple healing and healed tubercles of the liver and spleen.

Pathologic diagnosis: The final pathologic diagnosis was tuberculosis of the genitourinary tract with left pyelonephritis, bilateral pyelitis and ureteritis, acute and chronic cystitis, tuberculoma of the prostate, healed tuberculosis of the seminal vesicles, and uremia; active miliary tuberculosis of the lungs, healed miliary tuberculosis of the liver and spleen, tuberculoma of the left adrenal, and tuberculous ulceration of the ileum; and papilloma of the bladder. The cause of death was uremia due to extensive urinary tract tuberculosis.

In this case, uremia apparently resulted from obstruction of urine outflow due to tuberculous involvement of the pelves, ureters, and bladder with relatively little destruction of renal parenchyma. There was no evidence of secondary infection or of concomitant renal disease, but some obstruction to outflow from the bladder was present.

Case 2. L. W., a 65 year-old white male, entered the hospital with a three-week history of nocturia, frequency, difficulty in urination, and a thin urinary stream. There had been an 11 pound weight loss in the past month. Past history included a right epididymitis two and one-half years ago. The significant physical findings included an enlarged prostate and a tender, enlarged right epididymis. The blood pressure was 150 systolic, 90 diastolic in mm. of mercury.

A chest roentgenogram showed a cavity in the left upper lobe with exudative, productive lesions in both lung fields. The urine contained 15 to 20 leukocytes per high-power field. The blood urea nitrogen gradually rose from 85 to 115 mg. per 100 ml., and the creatinine from 4.8 to 6.0 mg. per 100 ml. The patient died on the eleventh hospital day. The final clinical diagnosis was far advanced pulmonary tuberculosis with tuberculosis of the genitourinary tract.

Post-mortem examination: At autopsy, the lungs showed bilateral upper lobe tuberculous cavitation with miliary spread throughout. Both kidneys were enlarged, the left more than the right. The capsules were adherent to the perinephric tissues and the renal surfaces. The left kidney showed thick yellow purulent material filling all of the calyces and the pelvis, greatly distending the kidney and stretching and thinning the renal parenchyma. The parenchyma was firm, white, and studded with small yellow abscesses. The ureter was dilated in the upper two-thirds, thickened and filled with purulent material; the lower one-third was narrowed and practically occluded by granular deposits. The mucosa of the pelvis and ureter was covered with yellow exudate. The right kidney showed a slightly narrowed cortex with numerous areas of necrosis. The calyces were moderately dilated; the pelvis was smooth and pale. The ureter was moderately dilated with a thickened wall covered with thin purulent exudate. The bladder was contracted with a thickened wall; the mucosa was gray and wrinkled. The lumen contained thick yellow mucopurulent material and a mass of green-yellow gritty material, 5 cm. in diameter. There was extensive caseation in the right testicle and seminal vesicle. The prostate was not enlarged, but contained firm nodular masses.

Microscopic examination: Microscopic examination showed caseous tuberculosis of the

lungs, tuberculous ulcerations of the bladder, and fibrocaseous tuberculosis of the prostate and epididymis and testicle. The kidneys showed productive tuberculosis, miliary tubercles, and pyelonephritis with papillary necrosis. There was nephrosclerosis classified as minimal to moderate degree of severity.

Pathologic diagnosis: The final pathologic diagnosis was bilateral far advanced fibrocaseous and cavitary pulmonary tuberculosis; genitourinary tuberculosis with left pyonephrosis, tuberculous stenosis of the left ureter, tuberculous pyelonephritis, right; and tuberculosis of the bladder, right epididymis, and right seminal vesicle.

In this case, uremia resulted from destruction of the left kidney by tuberculous pyonephrosis with subsequent tuberculosis of the right kidney. Some of the destruction of the right kidney was apparently due to superimposed secondary infection.

Case 3. C. B., a 53-year-old white female, had a right nephrectomy performed for tuberculous pyonephrosis three years before the present admission. Four months later her urine was positive for acid-fast bacilli, and a left ureterostomy was performed. Since that time, the patient has had several recurrent bouts of pyelonephritis with left upper quadrant abdominal and flank pain. Her final admission was for a similar episode of pain. The blood pressure was 140 systolic, 80 diastolic in mm. of mercury. The urine contained many erythrocytes and leukocytes. The hemoglobin was 7.9 gm. per 100 ml. The chest roentgenogram showed calcified foci in both apical regions. The blood urea nitrogen was 60 mg. per 100 ml. and the creatinine was 8 mg. per 100 ml. (blood chemistries performed during previous admissions were normal). The patient died on the eleventh hospital day. The final clinical diagnosis was: status postoperative right nephrectomy, left pyelonephritis with uremia.

Post-mortem examination: Post-mortem examination showed the right kidney to be surgically absent. The left kidney weighed 150 gm. The capsule stripped with difficulty. Cut section of the kidney showed the renal parenchyma to be almost completely replaced by green necrotic tissue, which in some places revealed solid white areas of necrosis. The ureter was markedly dilated and contained purulent exudate. The bladder mucosa was injected, and the lumen contained some purulent material. The lungs contained scattered small white foci, some of which were calcified. The other findings were not contributory.

Microscopic examination: Microscopic examination showed active tubercles in the lungs, tracheobronchial lymph nodes, and spleen. The kidney showed marked destruction with fibrous tissue replacement and infiltration of lymphocytes. There was some necrosis with surrounding epithelioid-like cells suggestive of tuberculosis. Marked necrosis of the papillary areas was present. Sections of the previously removed kidney showed definite tubercles. The pancreas showed definite changes of uremia.

Pathologic diagnosis: The final pathologic diagnosis was: status postoperative right nephrectomy (three years) and left ureterostomy (thirty-two months); tuberculous pyonephrosis with papillary necrosis and uremia.

The cause of death was tuberculous pyonephrosis with resultant uremia in a patient with a previous nephrectomy for renal tuberculosis.

Case 4. M. D., a 46-year-old white female, was admitted to the hospital because of urinary frequency, urgency, hematuria, and dyspnea. She first experienced these symptoms four years ago. At that time the left kidney was removed because of tuberculosis, and her symptoms subsided until two months ago when she again noted nocturia, hematuria, and dyspnea. No cough, hemoptysis, or night sweats were noted. The physical findings were not contributory.

The significant laboratory findings included: urine-specific gravity, 1.005; negative albumin, many leukocytes per high-power field. No acid-fast bacilli were found on microscopy or culture from the bladder on two occasions. The chest roentgenogram was normal. The intravenous urogram showed poor function of the right kidney, with considerable enlargement and distortion of pelvis and calyces; this was interpreted as tuberculous. The

blood urea nitrogen progressively increased from 54.5 mg. per 100 ml. on the day of admission to 135 mg. per 100 ml. at the time of death.

A right nephrostomy was performed on the fourteenth hospital day. No urine output occurred through the nephrostomy, although there was a fair amount through the ureter and bladder. The patient died on the twentieth hospital day and was in uremic coma for the last five days. The final clinical diagnosis was tuberculosis of the right kidney and bladder and uremia.

Post-mortem examination. The significant autopsy findings included: The left kidney was surgically absent; the right kidney weighed 250 gm. and showed considerable swelling. The capsule stripped with considerable difficulty, tearing the kidney parenchyma. On section, yellow rounded areas and glistening, definite puslike foci were noted in the region of the medulla and cortex. The cut surface was edematous and swollen. The pelvis was dilated and showed considerable thickening of the mucosa, with discoloration. The nephrostomy tube did not enter the pelvis but traversed the entire kidney parenchyma with the distal end appearing in the left peri-pelvic fat tissue. The ureter showed dilatation and considerable discoloration. The bladder was dilated and showed considerable discoloration of the mucosa, with thickened and hemorrhagic areas. The rest of the viscera showed no evidence of tuberculosis.

Microscopic examination: On microscopic examination the renal pelvis showed marked muscle hypertrophy and extensive inflammatory infiltration with ulceration. The kidney showed extensive alteration of architecture with prominent inflammatory cell infiltration and fibrosis. There was hyalinization of some glomeruli and hypertrophy of others, with dilatation of tubules. Some areas showed considerable inflamatory cellular infiltration, with isolated nodular grouping, central necrosis and epithelioid cells at the periphery suggesting distinct tubercles. Most of the remaining sections showed little nodular areas, although some foci of rounded hyalinosis suggested possible healed tubercles.

Pathologic diagnosis: The final pathologic diagnosis was chronic and acute pyelonephritis, tuberculous; chronic ureteritis; chronic and acute cystitis; edema of kidney and bladder.

Cases 3 and *4* represent instances of nephrectomy performed for renal tuberculosis, with subsequent development of contralateral renal tuberculosis. The remaining kidneys were largely affected by tuberculosis, but this destruction may well have been accentuated or accelerated by the secondary bacterial infection, possibly resulting from the operative procedures. Much of the potential reserve of renal parenchyma may have been sacrificed by the original nephrectomy.

Amyloidosis played no part in any of these cases. Some obstruction due to prostatic enlargement was present in *Case 1*. The minimal to moderate nephrosclerosis may well have been secondary to the pyelonephritis in *Cases 3* and *4* and probably contributed little to the uremia.

These 4 cases illustrate the rarity of uremia due to tuberculosis of the urinary system and emphasize that, when this entity occurs, there is frequently a loss of functioning renal parenchyma for other reasons, e.g., surgical removal of one kidney, secondary infection. It is also worth noting that the effect of benign nephrosclerosis may be difficult to estimate morphologically. Perfusion studies on such kidneys have shown that the vascular bed has become decreased by approximately 25 per cent in persons more than forty-five years old.

COMMENT

There are several possible explanations for the apparent rarity of uremia due to urinary tract tuberculosis. Small renal lesions may heal, leaving no residue or only small scars. Furthermore, small renal lesions of any degree of activity may easily be overlooked at autopsy. Many renal lesions are insignificant from the urologic point of view, e.g., miliary lesions and solitary caseous or calcific foci.

There is considerable protection afforded against uremia by virtue of the bilateral arrangement of the kidneys and ureters and the rarity of primary bladder tuberculosis, which could stenose both ureters simultaneously. Since one kidney lesion is usually more advanced and is clinically predominant, the process on the affected side directs the patient to seek therapy, and the disease may be controlled before bilateral involvement becomes extensive. Occasionally a far advanced lesion controls itself by "autonephrectomy."

To be severe, the renal involvement frequently requires a complication, and then relatively small kidney lesions can become significant. The chief urologic complication includes tuberculous stenosis of the calyces and/or ureters with secondary destruction and resultant extensive destruction of renal parenchyma, as may be seen in tuberculous pyonephrosis or a superimposed diffuse pyelonephritis, not specific but extensive, and sufficient to impair function slowly or rapidly.

The multiple unit structure of the kidney requires involvement of most of the renal pyramids to produce uremia. In tuberculosis this is accomplished best and most frequently by ureteral stenosis. This same mechanism similarly explains why obstruction of the ureters is a much more common mechanism of uremia than is replacement of renal parenchyma by tumor (4).

Although the initial seeding tuberculous renal lesion is more often cortical, the clinically significant areas of involvement are medullary. Once this occurs, progress is more rapid and destructive because of obstruction of individual calyces and/or ureters. This hydronephrosis destroys the cortical areas last, thereby preserving maximal renal function of filtration to the end.

The diminishing over-all frequency of tuberculosis of all organs, particularly the more extensive lesions, is due to increased public health measures and better control of the disease due to chemotherapeutic agents, and will further decrease the likelihood of uremia in the future. Chemotherapy is also effective by protecting the patient during surgical procedures. Furthermore, the rapid response of bladder mucosal lesions offers considerable security against spread to the opposite kidney.

Other factors which help to account for the apparent rarity of uremia due to urinary tract tuberculosis include the frequency with which these patients die of other forms of tuberculosis, e.g., pulmonary tuberculosis, tuberculous meningitis, et cetera, before sufficient time has elapsed to permit the development of bilateral far advanced renal disease. In addition, uremic symptoms and signs are often overshadowed by the infectious process itself with terminal wasting, cachexia, vomiting, coma, et cetera, or the clinician may fail to consider this entity because of the lack of emphasis noted in the literature.

Occasionally, secondary infection of tuberculous hydronephrosis may accelerate the tissue destruction, but many of the microorganisms which are apt to be involved are susceptible to present-day antimicrobial agents. Thus, the patient is afforded additional protection against complete renal destruction. The effective current medical and surgical therapy for such chronic suppurative tuberculous lesions as empyema and osteomyelitis will result in a diminution in the frequency and severity of amyloidosis, thereby eliminating another mechanism of uremia.

It is worth noting that many or all of the above factors frequently occur simultaneously or in varying combinations in individual instances to account for the over-all infrequency of uremia due to urinary tract tuberculosis.

Finally, it should be noted that the patient with tuberculosis is still subject to the other diseases which may be responsible for uremia, such as glomerulonephritis, and these must be considered and actively treated appropriately. Such diseases will attain greater significance with progressively better control of tuberculosis.

SUMMARY

Four cases of uremia due to urinary tract tuberculosis were observed in a series of 8,154 consecutive cases examined at autopsy at a general hospital from 1935 to 1949, inclusive. The failure of textbooks to mention or discuss this entity and the paucity of such cases in the current literature are noted.

The possible factors in various combinations responsible for the apparent rarity of this occurrence include the insignificance of many types of renal lesions, the bilateral arrangement of the kidneys and ureters and the rarity of primary bladder tuberculosis, the protection of the kidney due to its multiple unit structure, and the role of obstruction of the pelvic calyces and the ureters. Additional factors are: the diminishing frequency of tuberculosis in general; the effect of chemotherapeutic agents active against tubercle bacilli; the effect of death due to tuberculosis of other organ systems; the possibility of overlooking the occurrence of uremia because of failure to consider this entity or because of the severity of concomitant symptoms; the diminishing frequency of amyloidosis; and the control of secondary infections of the urinary system.

Some of these factors may be expected to result in a further diminution in the frequency of uremia due to urinary tract tuberculosis.

SUMARIO

Uremia Debida a Tuberculosis del Aparato Urinario

En una serie de 8,154 casos consecutivos autopsiados en un hospital general de 1935 a 1949, inclusive, se observaron 4 casos de uremia debida a tuberculosis del aparato urinario. Hácense notar la omisión de toda mención o discusión de esta entidad en los tratados de medicina y la escasez de estos casos en la literatura corriente.

Discútense los posibles factores en varias combinaciones que ocasionan la aparente rareza de esta situación. Comprenden los mismos la insignificancia de muchas formas de lesiones renales, la disposición bilateral de los riñones y los uréteres y la rareza de la tuberculosis primaria de la vejiga, la protección derivada por el riñón de las múltiples unidades que lo componen, así como el papel de la oclusión de los cálices pelvianos y los uréteres.

Nótanse la frecuencia ya menor de la tuberculosis en general, el efecto de los agentes quimioterapéuticos activos contra los bacilos tuberculosos y el efecto de la muerte debida a tuberculosis de otros sistemas de órganos. También se discuten la posibilidad de la ocurrencia de uremia debido a no considerarse esta entidad o a la gravedad de los síntomas concomitantes, a la frecuencia decreciente de la amiloidosis y al dominio de las infecciones secundarias del aparato urinario.

Cabe esperar que algunos de estos factores den por resultado una disminución aun mayor de la frecuencia de la uremia debida a tuberculosis del aparato urinario.

RESUME

Urémie par tuberculose des voies urinaires

Quatre cas d'urémie par tuberculose des voies urinaires ont été observés dans une série de 8.154 cas consécutifs autopsiés dans un hôpital général de 1935 à 1949 inclusivement. L'auteur signale que les manuels s'abstiennent de mentionner ou d'étudier cette entité ainsi que la rareté des cas publiés.

Les facteurs possibles et diversement combinés responsables de la rareté apparente de ce syndrome sont commentés. Ces facteurs comprennent : le peu d'importance de nombreux types de lésions rénales, la disposition bilatérale des reins et des uretères et la rareté de la tuberculose vésicale primitive, la protection du rein due à sa structure par unités multiples ainsi que le rôle d'obstruction des grands calices et des uretères. La réduction de la fréquence de la tuberculose, en général, le résultat de l'activité des agents chimiothérapeu-

tiques contre les bacilles tuberculeux et l'effet de la mort par tuberculose sur les autres systèmes organiques sont indiqués. L'eventualité de l'urémie soit parce que ce diagnostic n'a pas été envisagé ou en raison de la gravité des symptômes concomitants, ainsi que la réduction de la fréquence de l'amyloidose et le contrôle des infections secondaires des voies urinaires sont également commentés.

Il y a lieu de penser que certains de ces facteurs entraîneront une nouvelle diminution de la fréquence de l'urémie par tuberculose des voies urinaires.

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Notes

STREPTOMYCIN, ISONIAZID, AND PARA-AMINOSALICYLIC ACID IN THE TREATMENT OF PULMONARY TUBERCULOSIS

The intermittent multiple-drug regimens of streptomycin-PAS, streptomycin-isoniazid, and isoniazid-PAS are known to have a relatively high degree of effectiveness in the treatment of tuberculosis. The effectiveness is judged in terms of achieving a state of inactivity of the disease by the usual criteria of roentgenographic stability, reversal of infectiousness (sputum "conversion"), and closure of cavities. However, by the absolute criteria of closure of all cavities and sterilization of all lesions, it is recognized that the appropriate chemotherapy has not yet been discovered.

To see if some definite advantage might be derived from the use of a triple-drug regimen, a study was initiated at this hospital two years ago. Preliminary reports on the study have been given.[1] The present report consists of an evaluation of the regimens based on the experience in all patients who have completed eight months of treatment for pulmonary tuberculosis.

Patients were selected who had moderately advanced or far advanced pulmonary tuberculosis by the 1952 nomenclature of the National Tuberculosis Association. The patients represented consecutive admissions to this hospital and it was known that all would be available for treatment for at least an eight-month period. There was no randomized contemporary control group of patients.

No patient was accepted for the study who had received more than thirty days of chemotherapy prior to admission to the study.

All patients selected had sputum positive for tubercle bacilli on culture, or they were subsequently dropped from the study and do not appear in the statistical evaluations. Three patients were excluded because the microorganisms isolated were atypical for *M. tuberculosis*.

Six patients were eliminated from the study because of hypersensitivity to one or more of the drugs employed, and 12 were eventually dropped because of their inability to tolerate PAS.

Streptomycin or a streptomycin-dihydrostreptomycin mixture was given in a dose of 2 gm. every third day for the first six months, and was then reduced to 1 gm. every third day. Isoniazid was given in a dose of 300 mg. daily. Twelve grams of PAS were given daily.

Standard postero-anterior chest roentgenograms and apical views were obtained at four-, six-, and eight-month intervals, and were evaluated by a jury of three physicians. Roentgenographic clearing was interpreted in terms of *marked*, *moderate*, and *slight improvement*, *failure to improve*, or *worsening*. The behavior of cavities was evaluated and recorded separately.

Specimens of sputum were examined by microscopy and culture, or the gastric washings were cultured at intervals of two weeks. Gastric lavage regardless of presence of sputum was carried out at four, six, and eight months of therapy. Drug-susceptibility studies were carried out by the indirect method on all cultures positive for tubercle bacilli. American Trudeau Society medium was used and it contained streptomycin concentrations of 0, 1, 10, and 100 γ per ml.; PAS concentrations of 0, 1, 10, and 100 γ per ml.; and isoniazid concentrations of 0, 0.2, 1, and 5 γ per ml. After fourteen to twenty-one days of incubation, growth on each drug-containing medium was evaluated by comparison with a drug-free control tube of medium. Cultures which showed growth equal to the control in the presence

[1] WIER, J. A., *et al.*: Nat. Tuberc. A. Tr., 1954, p. 292.

TABLE 1

BACKGROUND OF PREVIOUSLY UNTREATED PATIENTS WITH RESPECTIVE THERAPEUTIC REGIMENS

Type of Disease	Streptomycin-PAS		Streptomycin-Isoniazid		Streptomycin-PAS-Isoniazid	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
	147	100	122	100	104	100
Moderately advanced	80	54	77	63	60	58
Far advanced	67	46	45	37	44	42
Bilateral	79	54	60	49	66	63
Unilateral	68	46	62	51	38	37
Cavitary	102	69	93	76	71	68
Noncavitary	45	31	29	24	33	32
New	113	77	109	89	85	82
Old	34	23	13	11	19	18

of streptomycin concentrations of 10 γ per ml., PAS concentrations of 10 γ per ml., or isoniazid concentrations of 5 γ per ml. were arbitrarily termed "resistant" to the given antibacterial agent.

The data on the background of this group of patients are shown in table 1. It may be seen from the tables, and it should be emphasized, that these patients as a group were ideal from the standpoint of recovery following treatment. For the most part they were soldiers in the vigorous prime of life and in excellent health prior to onset of their disease. Moreover, the disease was usually of relatively recent onset, and no previous therapy had been employed.

For purposes of comparison, the data obtained in previous studies in this hospital using intermittent[3] streptomycin-PAS and intermittent streptomycin-isoniazid regimens are included, both as to composition of the groups and as to results of treatment.

Roentgenographic evaluation: The number and percentage of patients whose pulmonary tuberculosis showed roentgenographic improvement, and the degrees of such improvement, are shown in table 2.

At four months of treatment, 45 per cent of the patients showed moderate or marked improvement, and at eight months this percentage had increased to 81.3 per cent. Slight improvement was noted in 16.6 per cent of the patients and the lesions in 2.1 per cent showed no change. There were no instances of worsening.

Of those patients with cavity at the start of treatment, 40 per cent of the 71 patients observed for four months had cavity closure as determined roentgenographically. At six months, 49.3 per cent of the 69 patients observed and, at eight months, 64.5 per cent of the 62 patients observed had experienced cavity closure.

As may be seen in table 3, the results obtained were comparable with those obtained previously with the dual-drug regimens, both in terms of clearing of roentgenographic densities and in terms of cavity closure. There was no striking advantage derived from the use of the triple-drug therapy.

The results of the bacteriologic evaluation are shown in tables 2 and 4.

At four months of treatment, reversal of infectiousness had occurred in 93.3 per cent

[3] The streptomycin was administered twice weekly; the PAS or the isoniazid was always given daily.

TABLE 2

ROENTGENOGRAPHIC AND BACTERIOLOGIC EVALUATION OF STREPTOMYCIN-ISONIAZID-PAS REGIMEN

Months of Treatment	4		6		8	
Total Number of Patients	104		98		96	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Moderate or marked clearing	47	45.2	68	69.4	78	81.30
Slight clearing	54	51.9	28	28.6	16	16.65
No change	3	2.9	2	2.0	2	2.10
Totals	104	100.0	98	100.0	96	100.00
Total patients with cavity	71	100.0	69	100.0	62	100.00
Cavity lost from view	29	40.0	34	49.3	40	64.50
Bacteriology						
Infectious at start	104	100.0	98	100.0	96	100.00
Reversal of infectiousness	97	93.0	96	98.0	93	97.00
Infectious	7	7.0	2	2.0	3	3.00

of the 104 patients with tubercle bacilli present in the sputum at the start of treatment At six months, reversal of infectiousness had occurred in 98 per cent of 98 patients. At eight months of observation, 97 per cent of 96 patients had attained the noninfectious status.

Of the 7 patients infectious at four months, one was still infectious at six months. The second patient who was infectious at six months had been noninfectious at four months. Both of these patients became noninfectious following six months of treatment.

The 3 patients who were infectious at eight months had been noninfectious at four and six months. One of these was infectious at seven months and subsequently noninfectious through twelve months. The second patient was infectious, and the tubercle bacilli isolated were resistant to all three drugs employed, after eight and one-half months of therapy; subsequently, this patient became noninfectious. The third patient was in-

TABLE 3

ROENTGENOGRAPHIC EVALUATION OF COMBINED STREPTOMYCIN-PAS-ISONIAZID

Regimen	Four Months			Six Months			Eight Months		
	Streptomycin-PAS	Streptomycin-Isoniazid	Streptomycin-PAS-Isoniazid	Streptomycin-PAS	Streptomycin-Isoniazid	Streptomycin-PAS-Isoniazid	Streptomycin-PAS	Streptomycin-Isoniazid	Streptomycin-PAS-Isoniazid
Number of patients	147	122	104	146	110	98	122	93	96
Moderate or marked improvement	33%	39%	46%	58%	66%	69.4%	66%	80%	81%
Cavity lost from view	26 of 103 or 25%	35 of 89 or 39%	29 of 71 or 40%	51 of 102 or 51%	51 of 82 or 62%	34 of 69 or 49.3%	55 of 90 or 61%	49 of 71 or 69%	40 of 62 or 64.5%

TABLE 4

BACTERIOLOGIC EVALUATION OF COMBINED STREPTOMYCIN-PAS-ISONIAZID

Regimen	Four Months			Six Months			Eight Months		
	Streptomycin-PAS	Streptomycin-Isoniazid	Streptomycin-PAS-Isoniazid	Streptomycin-PAS	Streptomycin-Isoniazid	Streptomycin-PAS-Isoniazid	Streptomycin-PAS	Streptomycin-Isoniazid	Streptomycin-PAS-Isoniazid
Number of patients	147	122	104	146	110	98	123	93	96
Culture negative for tubercle bacilli	129 (88%)	113 (93%)	97 (93%)	136 (93%)	105 (95%)	96 (98%)	116 (94%)	90 (97%)	93 (97%)
Culture positive for tubercle bacilli	18 (12%)	9 (7%)	7 (7%)	10 (5%)	5 (5%)	2 (2%)	7 (6%)	3 (3%)	3 (3%)
Strain drug-susceptible	16	6	6	8	3	2	6	2	1
Strain drug-resistant (streptomycin)	0	2	0	1	1	0	1	0	1
Strain drug-resistant (isoniazid)	0	1	0	0	0	0	0	0	1
Not available	2	0	1	1	1	0	0	1	1

Streptomycin resistance defined as growth in 10 γ per/ml. of culture media
Isoniazid resistance defined as growth in 5 γ per/ml. of culture media

fectious with drug-susceptible bacilli in the sputum at eight months, but subsequently became noninfectious throughout the remainder of the fourteen months of observation.

Another opportunity to evaluate the triple-drug therapy was provided by patients who had resection of tuberculous lesions of the lung. These were military patients who had received the triple-drug therapy and were treated until no further improvement was anticipated. Of these, 32 came to resectional surgery, either segmental or lobar. The usual indication for such surgery was the presence of residual roentgenographic densities interpreted as serious caseonodose residuals of disease. The average duration of chemotherapy was 9.1 months prior to surgery. The pathology reports of the tissue removed from these patients were reviewed to determine two features: (*1*) to see how many patients still had caseating granulomata present, and (*2*) to see if the lesions had been positive for acid-fast bacilli on microscopy.

The pathology reports on the tuberculous lesions removed from all of the military patients who received dual-drug therapy during the same period of time were likewise reviewed. There were 74 such patients, 70 of whom were treated with streptomycin-isoniazid, and 4 of whom received streptomycin-PAS.

Of the 32 patients who received triple-drug therapy, the resected lesions of 30 were positive for tubercle bacilli and contained caseonodose disease. In the resected specimen of one patient, no residual disease was found, and in one other specimen only pulmonary

TABLE 5

BACTERIOLOGY AND PATHOLOGY OF RESECTED SPECIMENS IN PATIENTS WHO RECEIVED DUAL-DRUG AND TRIPLE-DRUG THERAPY

	Dual	Triple
Number of specimens	74	32
Positive for acid-fast bacilli	69–93.2%	30–94.0%
Negative for acid-fast bacilli	5–6.8%	2–6.0%
Caseonodose disease	74–100.0%	30–94.0%
No caseous nodules found	0–0.0%	2–6.0%

fibrosis was seen. Of the 74 patients on dual-drug therapy, the lesions of 69 were positive for acid-fast bacilli; and caseonodose residuals were present in all specimens (table 5).

These figures conform with those of another study carried out at this hospital in which the specimens resected from all of the patients brought to surgery for caseonodose residual disease between the months of January and June, 1954, were studied for the presence of tubercle bacilli.[3] Of this group of one hundred and three patient-specimens, ninety-three (or 90.2 per cent) had acid-fast bacilli on microscopy of smears or histologic sections. In this study no difference was noted in the lesions from the patients who had received dual-drug or triple-drug therapy. It appears, therefore, that in this respect also triple-drug therapy offered no advantage over dual-drug therapy.

* * *

The response of tuberculous lesions of the lung to present methods of chemotherapy seems to depend greatly on the age and morphology of the disease. Recent lesions of principally exudative character for the most part clear dramatically and more or less completely. Older lesions, associated with varying degrees of caseation necrosis, excavation, and fibrosis, respond poorly and incompletely to chemotherapy. It might be simply stated that the success of chemotherapy lies in the ability to control recent exudative disease; to prevent further spread from caseonecrotic lesions; and to allow the body to proceed with its function of walling off and fibrosing the chronic nidus.

Available studies to date, from many sources, indicate that various chemotherapeutic regimens with the presently available drugs are very successful in achieving these objectives. Those regimens evaluated include daily streptomycin-PAS, intermittent[4] streptomycin-PAS, streptomycin-isoniazid, isoniazid-PAS, and streptomycin-PAS-isoniazid. Therapeutic differences among these regimens are slight and can be shown only in long-term large-scale randomized studies.

Significant differences probably depend upon the pathologic type of tuberculosis under treatment. For example, patients with chronic disease with multiple large cavities may respond more favorably to triple-drug therapy in terms of the eventual bacteriologic result.[5] Conversely, no such difference would be detected in the management of more acute, less destructive disease, whether the treatment be streptomycin-isoniazid-PAS, streptomycin-isoniazid, streptomycin-PAS, or isoniazid-PAS. The selection of therapy, therefore, might be determined in many cases by more practical factors, such as patient tolerance for the undividual drugs or unavailability of injectable drug.

Regardless of regimen, however, a problem that has not been solved is that of the caseonodose residual lesion which almost invariably contains tubercle bacilli which may be seen readily on direct smear or tissue stain. It appears, too, that with suitable technique a majority of such lesions yield organisms which can be grown.[6] There are no extended follow-up studies yet available to show how dangerous these caseous foci are after long-term drug therapy has been completed. Consequently, there is presently a sharp difference of opinion as to how vigorously the removal of these lesions should be approached.

[3] Adler, R. H., *et al.*: Tr. Fourteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, and Navy, 1955, p. 172.

[4] Unless otherwise specified, the streptomycin was administered two or three times weekly, whereas the PAS and the isoniazid were administered daily.

[5] Williams, J. H.: Tr. Fourteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, and Navy, 1955, p. 91.

[6] Hobby, G. L., *et al.*: Tr. Fourteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, and Navy, 1955, p. 180.

From the present review of the resected lung specimens from patients who had received triple-drug therapy for longer than eight months, it appears that nothing has been added to the solution of this problem by the use of triple-drug therapy with the three major antituberculous drugs in general use today. It might even be stated that the pathologic findings are a striking comment on the inadequacy of either the drugs used or the method by which they were used.

In summary: One hundred and four patients with moderately advanced and far advanced proved pulmonary tuberculosis who had not previously received drugs were treated with streptomycin twice weekly together with the daily administration of PAS and isoniazid. The response to treatment of these patients in terms of roentgenographic improvement, closure of cavities, and reversal of infectiousness was of an order previously seen with the dual-drug regimens, streptomycin-isoniazid and streptomycin-PAS. In specimens resected from patients suspected to have caseonodose residuals, tubercle bacilli were found readily, regardless of whether or not the patients had had dual-drug or triple-drug therapy prior to surgery. In view of these observations, it is concluded that it is not advantageous to use triple-drug therapy in the management of the instances of pulmonary tuberculosis usually seen at this hospital.

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July 27, 1955

PULMONARY RESECTION IN THE RABBIT[1]

The anesthesia and technique of pulmonary resection presented below were devised to study the effects of overdistension and possible subsequent emphysema on rabbit lung tissue containing bovine tuberculosis. The clinical aspects of this problem have long been a subject of controversy, and there is little experimental evidence available to clarify this issue (PAINE, J.: J. Thoracic Surg., 1940, *10*, 156).

The rabbit was selected in preference to other animals because the pathologic course of pulmonary tuberculosis in this animal has been carefully studied and is known to parallel the disease in man (MEDLAR, E. M.: Am. Rev. Tuberc., March, 1955 (Supplement)). According to Longacre and Johansmann (J. Thoracic Surg., 1940, *10*, 131), the effects of pneumonectomy have been studied in the dog, cat, and rat, but no reference to similar work in the rabbit could be found in the literature.

The rabbit is docile, clean, easily caged, and withstands pulmonary resections quite well. This procedure should, therefore, be practical in the study of other pulmonary diseases, in which progress may be followed with lung biopsies or serial resections.

The animals studied consisted of: 20 normal adult rabbits; 14 adult rabbits with miliary bovine tuberculosis, infected by intravenous inoculation, resected during and after cessation of chemotherapy; and 16 adult rabbits with bovine pulmonary tuberculosis, infected by inhalation, resected during and after cessation of chemotherapy.

The primary factor in obtaining a low mortality rate is good anesthesia. Endotracheal inhalation and intravenous barbiturate anesthesia were unsuccessful in preliminary attempts. The best results were obtained with open drop ether and positive pressure from the Dann Portable Resuscitator (figure 1*A*). This machine delivers oxygen, or a mixture of oxygen and ether, to the rabbit through an oral catheter and tight-fitting mask.

The rabbit was starved for twenty-four hours prior to operation, and 0.1 mg. of atropine sulfate was injected in the marginal ear vein immediately before induction. This helped reduce the secretions in the bronchial tree and diminished the possibility of a vagal reflex while manipulating the hilum.

Induction was performed with open drop ether while the animal was in a rabbit box (figure 1*B*). The rabbit went through the same stages and planes of anesthesia as does the human. However, the rabbit is quite labile and goes from light to deep anesthesia, and the reverse, quite rapidly.

When induction was complete, the rabbit was taken out of the box and placed on its side (figure 1*C*). Open drop ether was continued in this position until the surgical plane of anesthesia was reached. This was determined by the eye signs, which are remarkably accurate. However, the regularity and depth of breathing were more reliable signs in determining the level of anesthesia.

Open drop ether was used to maintain the level of anesthesia during the entire procedure, except while the chest was open. At that time, positive pressure oxygen or a mixture of oxygen and ether were used with 10 cm. of water pressure and a respiratory rate of 40.[2]

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[1] Presented before the Medical Session, as part of *Section 1B*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 23, 1955.

[2] A ten-minute Kodachrome 16 mm. sound film, illustrating the anesthesia and technique described above, is available through the Veterans Administration Hospital, Sunmount, New York.

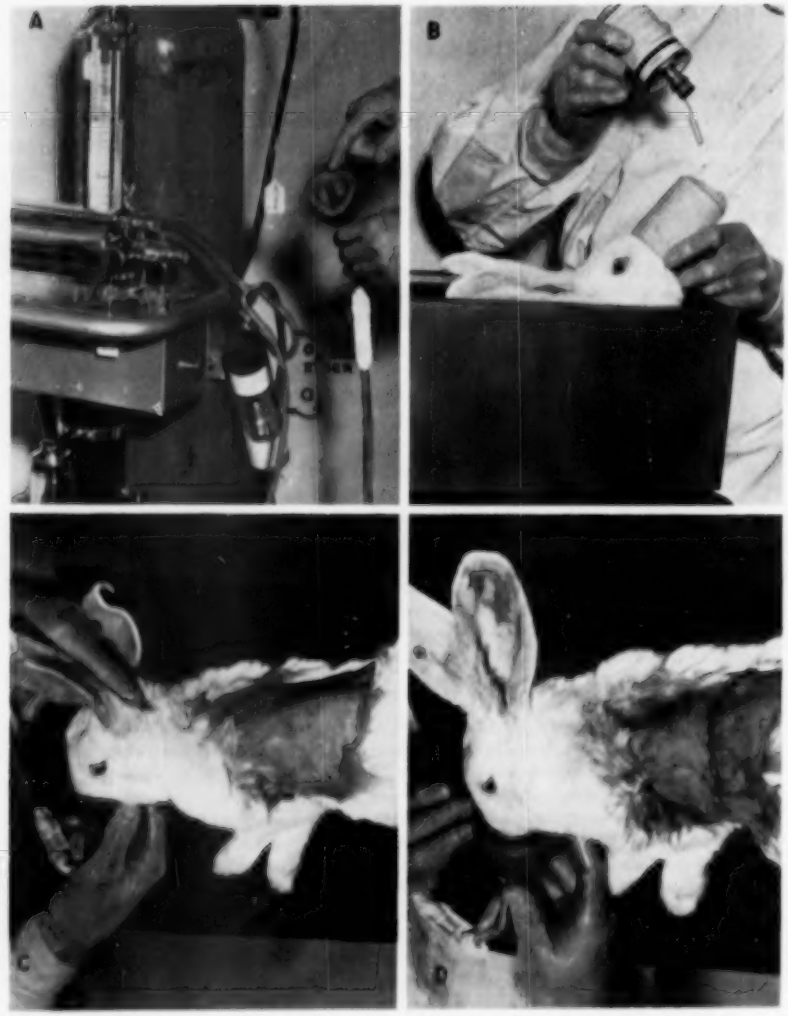

FIG. 1. *A*. The Dann Portable Resuscitator, made by the Dann Manufacturing Company, Cleveland, Ohio. *B*. Induction performed with open drop ether in a rabbit box. *C*. The rabbit in position for a left thoracotomy. *D*. The rabbit immediately after a left pneumonectomy.

When the rabbit was in the surgical stage of anesthesia, the skin which had previously been clipped was prepared with an antiseptic solution. Sterile technique is difficult to maintain; however, contamination was avoided as much as possible. Drapes were placed, and a modified parascapular incision made over the fourth interspace. Minimal bleeding

was encountered in opening the pleural cavity, and usually only two bleeding points in the subcutaneous tissue had to be arrested. The lattisimus dorsi and serratus anterior muscles were divided and the scapula retracted. At this point, positive pressure anesthesia was instituted and the pleural cavity was opened through the fourth intercostal space. The rib spreader was inserted and mobilization of the lung begun at the inferior pulmonary ligament, which is a filmlike structure and easily divided up to the hilum. The lung was then gently elevated between the fingers and the hilar structures visualized. A curved hemostat was placed across the hilum, and the lung was excised distal to it. A double fixation ligature of 2-0 silk was inserted proximal to the hemostat and carefully tied while the clamp was removed. Only one accident involving the slipping of this ligature has occurred; hence, resort to handling the hilar structures individually has not been made.

The blood was carefully sponged from the chest, and the ribs were approximated with three pericostal sutures of 00 chromic catgut. In older rabbits, heavier suture material was necessary because of the lesser resiliency of the ribs. The serratus anterior and lattisimus dorsi muscles were next closed with running 00 chromic catgut sutures.

The chest at this time was usually airtight and contained a positive intrapleural pressure. One-quarter of a gram of streptomycin and 100,000 units of penicillin were injected into the pleural cavity and the air was carefully aspirated until a rather strong negative pressure could be felt on the syringe. The positive pressure anesthesia was then removed and the rabbit kept under light ether analgesia until the skin was closed. A running 00 chromic catgut suture was used to approximate the skin edges.

Gastric distension caused by the positive pressure anesthesia could then be relieved by gentle manual compression of the abdomen.

Chest roentgenograms in the postero-anterior position were taken at the onset of chemotherapy (figure 2*A*), preoperatively (figure 2*B*), and immediately after operation and at weekly intervals until the mediastinum was stabilized (figures 2*C* and *D*).

A total of 50 rabbits was subjected to pneumonectomy, with a mortality rate of 25 per cent on the first 20 and 5 per cent in the last 30 animals.

Preliminary observations of remaining lungs in rabbits, sacrificed at three months following pneumonectomy, showed slight compensatory emphysema. Rabbits followed up to six months after pneumonectomy, and which had not received chemotherapy during this period, have been without evidence of tuberculous reactivation in the single lung.

The present experience has indicated that the rabbit withstands pulmonary resection quite well. It is suggested that selective pulmonary resection may be of value in the study of other chronic pulmonary diseases.

Most of the complications of the procedure occurred during induction of the anesthesia. Ventricular fibrillation was the most common, accounting for 75 per cent of the mortality. Cardiac massage and defibrillation revived one rabbit for twenty hours, but it has been difficult to combat the effects of hypoxia. Fracture of the lumbar spine also occurred, but can usually be avoided if the animal is compressed tightly in a rabbit box so that leverage for the hind legs is not provided.

Technical errors rarely occurred during operation. Hemorrhage caused only one death in the present series and that was in a rabbit which was undergoing a second lobectomy on the left side.

In the immediate postoperative period, one mortality resulted from a tension pneumothorax. The hilar ligature had slipped and air had leaked from the bronchial stump.

FIG. 2. Postero-anterior chest roentgenograms in rabbit No. 15. *A*. Showing miliary tuberculosis at the onset of chemotherapy. *B*. Six days prior to operation, showing clearing of the disease. *C*. One hour following a left pneumonectomy. *D*. Eight days after operation, showing the mediastinal shift to the left.

Empyema resulted in two deaths during the late postoperative period. Since penicillin and streptomycin had been injected into the thoracic cavity at operation, and had been continued intramuscularly for two weeks following resection, there were no chest wall or pleural infections.

In summary: A technique for pulmonary resection in the rabbit is presented. The anesthesia, technical points of the procedure, and complications are described in detail. This operation was devised to study the effects of overdistension and compensatory emphysema on miliary and inhalation bovine tuberculosis in the rabbit, both during and after cessation of chemotherapy.

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May 23, 1955

RESULTS OF AN INTERNATIONAL SURVEY OF PULMONARY TUBERCULOSIS

On returning from the Conference of the International Union Against Tuberculosis, held in Madrid in the fall of 1954, an attempt was made to analyze the reports presented with the hope of determining the facilities for hospitalization and the treatment used for pulmonary tuberculosis in each of the countries represented. With a few exceptions, this was not possible because of the character of the reports presented.

Accordingly, it was decided to conduct an international survey of tuberculosis therapy by mail, covering countries in addition to those affiliated with the International Union. Correspondents were selected from such sources as the roster of the American Trudeau Society (including particularly the Corresponding Members in foreign countries), delegates to the recent meeting of the International Union, officers of tuberculosis associations, et cetera. A letter requesting the desired information and explaining the purpose of the survey, with an outline of subjects to be covered, was mailed to these correspondents on the stationery of the American Trudeau Society[1] about January 1, 1955. Correspondents were requested to indicate when methods of therapy differed appreciably in various regions within their own countries.

Replies were received from 31 of 60 correspondents to whom letters were sent.[2] In addition, it was possible to include information in the final tabulation gleaned from a few of the reports given at the Congress of the International Union in Madrid and from the 1954 and 1955 meetings of the Committee on Chest Surgery and Collapse Therapy of the International Union. Information received during a recent trip to Mexico was also included.

Although the response to the survey was incomplete from a numerical standpoint, the geographical distribution of the reports received was good. Some of the replies received were extremely comprehensive, even though the correspondents had been told that they need not be lengthy. It is regrettable that some of these interesting reports cannot be published in full.

The first point on which information was requested was in regard to the *adequacy of hospital and sanatorium facilities* for active cases of tuberculosis. The replies to this inquiry were tabulated as follows:

Adequate or excess beds: Great Britain (excess in one area), Ireland (excess), Holland (700 excess in total of 9,200), Switzerland (excess).

Beds almost adequate: Finland, Belgium, West Germany, Poland, Spain, Portugal, New Zealand, Trinidad, Peru, Uruguay (shortage of 200 beds for women, excess of

[1] Dr. Steele was then president of the American Trudeau Society. (*The Editor*)

[2] The thirty-one correspondents were: *Great Britain*, Dr. R. Y. Keers; *Ireland*, Dr. James A. Deeny; *Finland*, Dr. Erkki Larmola; *Belgium*, Dr. H. Durieu; *Holland*, Dr. C. Banning; *Switzerland*, Dr. J. Morin; *West Germany*, Prof. Kurt Lydtin; *Poland*, Prof. Dr. Janina Misiewicz; *Russia*, Prof. N. A. Schmeler; *Spain*, Dr. Joaquin Marquez-Blasco; *Portugal*, Prof. Lopo de Carvalho; *Jordan*, Dr. Jirair H. Arsenian; *Egypt*, Dr. Taha M. Gomaa; *Iraq*, Dr. Najib Mahmoud; *India*, Dr. B. S. Verma; *Burma*, Dr. Than Aung; *Malaya*, Dr. L. Sammy; *Indonesia*, Dr. Johannes G. Wisse; *New Zealand*, Dr. Adrian H. Webb; *Hong Kong and South China*, Dr. R. Tak Eng; *Formosa*, Dr. Jung Chin Tao; *Japan*, Dr. Masatoshi Shiozawa; *Jamaica*, Dr. Richard A. S. Cory; *Trinidad*, Dr. W. J. Branday; *Costa Rica*, Dr. R. Blanco Cervantes; *Panama*, Dr. A. V. Mastellari; *Peru*, Prof. Oridio Garcia; *Paraguay*, Dr. Juan M. Boettner; *Uruguay*, Prof. Fernando D. Gomez; *Argentina*, Dr. Raul F. Vaccarezza; *Chile*, Prof. Dr. H. Orrego Puelma.

300 beds for men), Chile (beds for women almost adequate, shortage of beds for men).

Inadequate beds: Jordan, Egypt, Iraq, India, Burma, Malaya, Indonesia, South China, Formosa, Japan, Mexico, Jamaica, Costa Rica, Panama, Paraguay, and Argentina.

Excerpts from some of the replies in regard to the adequacy of beds follow:

Poland: "Sanatorium facilities are sufficient for the hospitalization of most active cases; delay in hospitalization varies from 3 to 6 weeks. There is a scarcity of beds for chronic patients who wait for admission for 2–3 months. There is no excess of beds, in spite of the fact that 10,000 sanatorium beds were established in the years 1946–1954."

Russia: "The treatment of the actively ill forms of tuberculosis is conducted in special clinics in dispensary stations. In view of the fact that, at the present time, sanatoria have begun utilizing all phases of complex treatment, not only chemotherapeutic, but surgical methods as well, patients with active tuberculosis are placed not only in hospitals of various types but also in sanatoria. Under the single government system of medical aid in the U.S.S.R. the number of beds allotted to any given form of the disease is governed by the necessity of the moment. In case an excess of beds exists for a given form of tuberculosis, the excess is then assigned to the type of tuberculosis in which there is a lack of beds. In view of early diagnosis and the early beginning of treatment, the character of the curative establishments changes depending on the profile of the hospitalized patients."

Jordan: "Sanatorium facilities are available, but the total bed capacity is hardly sufficient for the hospitalization of more than 20 per cent of all known active cases. General hospitals have been accommodating tuberculous cases for the management of hemoptysis, spontaneous pneumothorax or empyema but only for short periods. The larger fraction of active cases has to be treated at home."

Egypt: "The incidence of pulmonary tuberculosis (active cases) in Egypt according to mass radiographic studies, done during the last five years, shows that it varies between 0.7–1.1 per cent of the whole population of 22 millions.[1] The number of beds for tuberculosis is far from being adequate. Until the end of 1953, there were only 3,770 beds in the whole country. But, by the end of 1954, the total number of beds did rise to 5,000; and it is estimated that by the end of 1956 this figure will rise to 8,000 beds."

Iraq: "The first chest hospital in Iraq, the Prince Abdul Ilah Chest Hospital, built in 1950, can receive about 750 patients. The hospital has special rules and regulations for admitting patients, and hundreds of patients are on the waiting lists, and many pass away before they have the chance for admission. Out of every 100 patients I have examined, 10 have active tuberculosis, proved by laboratory and X-ray examination."

India: There are 500,000 deaths from tuberculosis per year and only 18,000 available beds.

Burma: "Rangoon and Mandalay are the only two cities in Burma which have any special facilities for the hospitalization of pulmonary tuberculosis patients. Rangoon with a population of over 700,000, with an estimated tuberculosis morbidity rate of 4.55 per cent for all age groups, has some 300 beds for the treatment of pulmonary tuberculosis. Mandalay, the next largest city, with a population of some 200,000, has only 30 beds in the General Hospital."

[1] Roughly, 220,000 cases.—*Ed.*

Indonesia: "It is estimated that 2 per cent of the population of 80,000,000 have active tuberculosis. There are 1,600 beds in 15 sanatoria."[4]

Hong Kong and South China: "In Hong Kong, 95 per cent of the cases are ambulatory; hospital beds are reserved for the operative and acute cases. There is no tuberculosis hospital in Canton (Communist China) other than our Chest Clinic Hospital of 30 beds."

Formosa: "There are only 500 beds available for civilians, while the annual deaths are as many as 12,000 (mortality rate 150 per 100,000). It is expected that 500 more beds will be added in the near future but, even so, the bed capacity is extremely outproportioned for the purpose of the isolation of most infectious cases, and the current policy for admission is to admit open cases for surgical treatment or for short-term stay to initiate pneumotherapy or chemotherapy."

Japan: "The number of tuberculosis patients in Japan is extremely large. The survey of tuberculosis incidence among the entire population (by random sampling method) revealed the following results:

a. Number of persons requiring medical care (6.4% of entire population)	5,530,000
Persons requiring immediate treatment	2,920,000
Persons requiring rest	320,000
Persons requiring caution	2,290,000
b. Number of persons requiring hospitalization	1,370,000
Chemotherapy	510,000
Surgical therapy	420,000
Artificial pneumothorax and pneumoperitoneum	30,000
Rest and symptomatic therapy	410,000

Although the number of beds is increasing yearly, this number can accommodate only 10 per cent of the patients requiring hospitalization and 25 per cent of the reported patients. There were 151,072 beds in 1952."

* * *

When reporting on the use of *antimicrobial therapy,* correspondents were asked to list the drugs in general use, the combinations of drugs used, and the minimum and maximum length of courses. An estimate of the use of drugs in home treatment, with and without sanatorium care, was also requested.

Correspondents from the following countries reported the use of streptomycin, isoniazid, and para-aminosalicylic acid (PAS) in doses and regimens quite similar to those currently being used in the United States, without noteworthy exceptions: Spain, Portugal, Jordan, Iraq, Burma, Malaya, Indonesia, New Zealand, Mexico, Jamaica, Trinidad, Costa Rica, Panama, Paraguay, and Argentina.

Interesting variations, either in the use of different drugs or regimens, were noted in the reports of the following countries:

Great Britain: About 40 per cent of phthisiologists use daily streptomycin with daily isoniazid. PAS often is used in a dose of 20 gm. per day. (One Irish sanatorium uses 18 gm. per day.)

Belgium: Isoniazid is reserved for patients whose bacilli are not susceptible to PAS, and for miliary and pneumonic lesions. Isoniazid-PAS combination is rarely used.

Switzerland: A sulfone (Di-Atox) is used in addition to streptomycin, PAS, and isoniazid in various combinations. Duration of chemotherapy is generally six months.

[4] This means that for the 1,600,000 with active tuberculosis there is one bed for every one thousand potential patients.—*Ed.*

Poland: Isoniazid-PAS and streptomycin-PAS regimens are used alternately in chronic disease. For example, first and second months, streptomycin-PAS; third, fourth, and fifth months, isoniazid-PAS; sixth month, streptomycin-PAS. All three drugs are used simultaneously in active disease.

Russia: In addition to streptomycin-PAS, a derivative of isonicotinic acid hydrazide, "Phtivazid," is given in small doses, 0.3 to 0.6 gm. per day, in "early forms of tuberculosis not presenting an established focus" and in larger doses, 1.0 to 1.5 gm. per day in "active forms." Duration of chemotherapy varies between four and nine months, although second courses of two or three months' duration are given if there is any sign of recurrent activity.

Ireland, Finland, West Germany, Russia, and *Spain* were the only countries reporting the continued use of amithiozone (TBI) either alone or in combination with other drugs.

Egypt: The average duration of chemotherapy is two months. A few more severe cases receive treatment for one year.

India: The combination of isoniazid and PAS is rarely used, although isoniazid is used frequently with streptomycin.

China: The correspondendent stated that, in his experience, the Chinese do not tolerate PAS well.

Japan: "The Committee of the Chemotherapy of Tuberculosis of the Health and Welfare Ministry of Japan has made a comparative study of the effect of INH and PAS daily treatment and that of the INH semi-weekly and PAS daily treatment. It was revealed by the study that the INH daily regimen is superior to the INH semi-weekly regimen for improvement of the rate of X-ray findings and also in the negative conversion rate of tubercle bacilli in sputum, but that the INH-resistant tubercle bacilli were discovered more often in the daily regimen than in the semi-weekly one. It was recommended by the Committee of Chemotherapy of Tuberculosis that the daily use of INH might be continued as long as the symptoms of the patient are severe, but that it must be changed to the semi-weekly regimen as early as possible if the symptoms of the patient become less severe. Six months is the standard duration of treatment."

Uruguay: Isoniazid is given twice weekly. It is believed that the results are as good as when it is given daily.

Chile: This was the only country to mention the use of isoniazid alone in ambulatory patients.

A question was also asked in regard to laboratory resistance or loss of drug susceptibility and whether any particular *in vitro* level was regarded as clinically significant. Replies to this question were fairly uniform and, generally, were in accord with the views held on this subject in the United States.

* * *

Correspondents were asked next to estimate the frequency of the use *of collapse therapy procedures* currently employed. A tabulation of their replies follows:

Phrenic Paralysis

Use abandoned or used rarely: Great Britain, Norway, Finland, Belgium, Holland, Switzerland, Russia, Spain, Portugal, Burma, Indonesia, Formosa, Costa Rica, Paraguay, and Chile.

Use diminishing or relatively infrequent: West Germany, Poland, Spain, Jordan, India, New Zealand, South China, Japan, Jamaica, Uruguay, and Argentina.

Still used frequently: Ireland (in some sanatoriums—rarely in others), Egypt, Iraq, Malaya, and Trinidad.

Pneumothorax

Use abandoned or used very rarely: Great Britain, Norway, Holland, South China, Mexico, Jamaica, Costa Rica, Panama, Peru, and Paraguay.

Use diminishing or relatively infrequent: Ireland, Finland, Belgium, West Germany, Poland, Jordan, New Zealand, Formosa, Japan, Uruguay, and Chile.

Still used frequently: Switzerland, Russia, Italy, Spain, Turkey, Egypt, Iraq, India, Burma, Malaya, Indonesia, Trinidad, and Argentina.

Pneumoperitoneum

Inadvertently, no information was requested in regard to the use of pneumoperitoneum. However, a number of correspondents volunteered information in regard to this procedure. It is used frequently in Turkey, Jordan, Egypt, Malaya, South China, Paraguay, and Uruguay; it is not used in West Germany and Formosa; it is used in Argentina for basal disease only.

Extrapleural Operations (mostly extrapleural pneumothorax)

Used frequently in West Germany, Russia, Italy, and Spain. Used relatively infrequently in Finland, Belgium, Switzerland, Poland, and Turkey.

Used occasionally in Iraq, New Zealand, Japan, Jamaica, Costa Rica, and Argentina.

Extrapleural Plombage

The following countries reported the use of this procedure with varying frequency: West Germany, Russia, Spain, Iraq, India, Indonesia, South China, Jamaica, Panama, Uruguay, and Argentina. Spain, Iraq, and Indonesia specified that "polystan" was used as the medium for filling.

Cavity Drainage

Ireland, Spain, Iraq, India, Jamaica, Chile, and Argentina reported use of this procedure in rare cases.

Definitive Thoracoplasty

Used frequently in Great Britain (except for 2 areas), Ireland, Norway, Finland, Belgium (except in a few centers), Switzerland, France, Russia, Italy, Spain, Portugal, Turkey, Egypt, Iraq, Malaya, Burma, New Zealand, Formosa, Japan, Mexico, Jamaica, Trinidad, Paraguay, Uruguay, Argentina, and Chile.

The procedure is used infrequently or not at all in Holland, West Germany, Poland, Indonesia, South China, Costa Rica, Panama, and Peru. (In some countries the use of thoracoplasty has been completely replaced by resection; in others, various other collapse therapy procedures are preferred.)

Finally, a request was made for the indications for *resection*. The replies were so varied that an accurate tabulation has not been possible. In a few countries no reply to this question was possible because of a complete absence of surgical facilities. However, an inquiry whether residual necrotic foci are being resected following long-term chemotherapy did yield some rather interesting replies.

The following countries are definitely opposed to, or extremely reluctant to use, resection of residual necrotic foci following long-term antimicrobial therapy: Finland, Switzerland, Spain, Egypt, Costa Rica, and Uruguay. Excerpts from the replies of other correspondents follow:

Great Britain: "The resection of residual necrotic foci gave rise to various opinions. In some areas any focus of 1.5 cm. in diameter was removed. In others the focus had to be at least 2 cm. or more before resection was advised. Multiple resections were not favored and one or two physicians expressed the view very strongly that they preferred the surgeon to resect only the selected segment containing the main focus, leaving untouched the minor foci known to be present in the adjacent areas which they felt could be dealt with satisfactorily by chemotherapy."

Ireland: "Some institutions resect necrotic foci when there is danger of reactivation."

Indonesia: "We are not resecting residual necrotic foci following long-term chemotherapy because our mortality is still high (almost 10 per cent)."

New Zealand: "It is not at all uncommon to resect a necrotic focus following prolonged chemotherapy."

Japan: "Sputum negatives having caseous lesions 2 cm. in diameter, inspissated cavities, or groups of small lesions are indicated for pulmonary resection not by all doctors but by some; and I am one of the latter, because when resected materials were examined, the bronchocavitary junction was open and culture of tubercle bacilli was positive in more than 50 per cent of those cases; it is quite difficult to determine clinically in which lesions the bronchocavitary junction is open, or the culture of tubercle bacilli is positive. The resection of residual necrotic foci following chemotherapy is also indicated according to size, namely more than 2 cm., sometimes even 1.5 cm. in diameter. In the sanatoria of the Japanese Anti-Tuberculosis Association in 1954, 314 segmental resections were performed as compared to 98 lobectomies, 2 pneumonectomies, and 60 thoracoplasties."

Paraguay: Residual foci are resected only in those cases which have relapsed.

Chile: "Surgical services in countries which still have high morbidity and mortality from tuberculosis should concentrate on the treatment of active cases rather than on those whose activity is doubtful."

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"COIN" LESIONS OF THE LUNG[1]

This paper is a report on a series of "coin" lesions. The danger of these lesions and the difficulty of diagnosis without thoracotomy are emphasized.

The first "coin" lesion of the lung was reported in 1883 by Chiari[2] who described this abnormality as a peripheral chondroma. Graham[3] initiated the surgical treatment of the peripheral circumscribed lung lesion in 1925 by thoracotomy and excision of a tuberculoma. He excised similar lesions in 1935 and in 1936. Subsequent reports have described the incidence and nature of "coin" lesions which are usually either early carcinomas or dangerous inflammatory foci.

It is difficult to define the pulmonary "coin" lesion, for there are as many definitions as there are reports. Some writers state that a "coin" lesion has no size limitation and that it may be termed "coin" if it is well circumscribed. Others state that a limitation of size is necessary. As a silver dollar is 4 cm. in diameter, it seems natural to limit the maximum diameter of a "coin" lesion to that diameter. The criteria for inclusion in the present series were as follows:

1. A diameter between 1 and 4 cm.
2. A well-circumscribed tumor
3. A lesion surrounded by lung
4. No evidence of major bronchial obstruction

Excavating lesions and lesions associated with other lung abnormalities were excluded.

A review of the literature shows that 729 pulmonary "coin" lesions have been reported. The present report adds 124 such lesions found in various age groups. The cases were selected by reviewing the files from the services at the Allegheny General Hospital and the University of Pittsburgh Medical Center Hospitals. The roentgenograms were reviewed to ensure that the cases fulfilled the criteria given above. All of the lesions were encountered in the four-year period between January, 1951, and January, 1955.

There was no operative mortality in the series. Forty-three (73.05 per cent) of the 59 benign lesions were removed by wedge resection, and 5 (8.49 per cent) were excised by segmental resection. Lobectomy was technically necessary in 11 (18.64 per cent) of the benign tumors).

In the tumor group, lobectomy was also done in 9 cases (13.04 per cent). Included in this group of lesions were 5 bronchial adenomas, 3 bronchogenic carcinomas, and one metastatic melanoma. It was believed that pulmonary invalidism would occur if pneumonectomy were performed in the 3 aforementioned carcinoma patients. Fifty-six (86.16 per cent) of the malignant lesions were treated by total pneumonectomy.

In table 1 are listed the series of "coin" lesions found in the literature in which all of the lesions were examined histologically and classified accordingly. The benign and malignant lesions (which include bronchial adenoma) have separate listings. The sarcoma classification in the table includes neurogenic sarcoma and lymphosarcoma. Chest wall tumors, broncholithiasis, and circumscribed intrathoracic lesions caused by diaphragmatic hernias, aortic aneurysms, mediastinal cysts, and dermoid cysts were excluded from the tabulation.

[1] Presented before the Medical Session, as part of *Section 4A*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 24, 1955.

[2] Chiari: Prag. med. Wchnschr., 1883, *8*, 497.

[3] Graham, E. A., and Singer, J. J.: J. Thoracic Surg., 1936, *6*, 173.

In table 2, the present series of 124 excised "coin" lesions is presented. Twelve histologically different lesions were found. Fifty-nine (47.5 per cent) of the 124 lesions in the series were bronchogenic carcinoma. Three patients with bronchogenic carcinoma were roentgenographically acceptable for surgical therapy but were found to have inoperable mediastinal metastases at the time of thoracotomy. These cases were excluded from the series. It was remarkable that the remaining 59 bronchogenic carcinomas did not show gross mediastinal extension. Six other malignant lesions included 5 bronchial adenomas and one metastatic melanoma.

A later study is planned to present the five-year postoperative study of the patients in whom these lesions were detected.

Forty-two (71.19 per cent) of the benign lesions were granulomas. These were thought to be tuberculomas but were classified as nonspecific granulomas, for no effort was made to culture fungi or tubercle bacilli from the specimens. The 7 lesions classified as tuberculomas had the typical calcific laminations with a caseous center. It is recognized that the roentgenographic finding of scattered calcification in a lesion usually points to its being benign. Nevertheless, it must be recognized that malignant tumors, such as carcinomas, sarcomas, and adenomas, may be calcified. In the present series there were 5 bronchial adenomas and one each of the following lesions: bronchial cyst, chondroma, arteriovenous aneurysm, lipoid pneumonia, and metastatic melanoma.

In table 3 the danger of the "coin" lesion is emphasized. The incidence of malignancy in such lesions ranges from 7.94 per cent in the series reported by Mahon and Forsee[4] to an incidence of 73.91 per cent in Thornton's series.[5] The former study, however, was based on patients hospitalized for treatment of pulmonary tuberculosis and, thus, was not a group representative of the general population.

Approximately 40 per cent of the group of 59 patients in the present study found to have benign lesions were more than forty years of age. In the group of 65 patients proved to have malignant pulmonary lesions, approximately 90 per cent were more than forty years of age and only 10 per cent fell into age groups of forty years or less. Of the patients forty-one years of age or older with "coin" lesions, approximately 66 per cent were found to have malignant lesions. The average age of the patients with malignant "coin" lesions was fifty two years, with an inclusive range from thirty-five to seventy-six years of age. Bronchogenic carcinoma occurred approximately nine times more frequently in males than in females. The ratio of the sexes among the patients presenting proved benign pulmonary "coin" lesions was three males to one female.

Signs and symptoms that may be caused by the "coin" lesion include cough, clubbing of the digits, hemoptysis, intermittent fever, joint pain, wheezing, and fatigue. In the present series, 87 of the 124 patients (70 per cent) complained of a chronic cough. This symptom was probably not caused by the "coin" lesion in many cases. Digital clubbing was found in six (10.18 per cent) of the carcinoma patients. Clubbing was not evident in any of the patients with benign lesions except the patient with a pulmonary arteriovenous fistula. Thirty (24.11 per cent) of the total group gave a history of hemoptysis. Twenty-four of these patients had bronchogenic carcinoma and 3 had bronchial adenomas. The remaining 3 patients had benign lesions. Of this group, 2 had granulomas and the third had an arteriovenous fistula. Intermittent fever, joint pain, wheezing, and fatigue were not recorded as symptoms.

The circumscribed lung lesion, limited in size and located in the periphery, does not lend itself to diagnosis by bronchoscopy; therefore, this procedure was not routinely done. Bronchography is not thought to be important in diagnosing the "coin" lesion. Laboratory studies were of little assistance in diagnosis; however, their exclusion is not recommended. Routine admission studies were not helpful and a sedimentation rate above 20

TABLE 1

"COIN" LESIONS OF THE LUNG

(Listed in order of frequency)

	Hood, *et al.*[4]	Grow, *et al.*[7]	Davis and Klepser[8]	Mahon and Forsee[1]	Fink and Asta[9]	Sharp and Kinsella[10]	Storey, *et al.*[11]	Condon[12]	Effler, *et al.*[13]	Husfeldt and Carlsen[14]	Wolpaw[15]	Bell and Sealy[16]	Thornton, *et al.*[2]	O'Brien, *et al.*[17]	Abeles and Ehrlich[18]	Effler[13]	Hare and Battersby[19]	Total	Percentage
Benign (histologically proved):																			
Tuberculoma		37	17	48	19	11	28	2	7	2	7	10	4	8	5	8	1	214	
Granuloma (nonspecific)	65		1		4	1	1				3	1						76	
Hamartoma	25	1		1	8	5	2	4	1	5	2					1		55	
Bronchial cyst	4	13	2	1	3	8		1	6	4		1		1				44	
Pneumonitis, chronic	1		5	1		10											1	18	
Fibroma			5			2			1		1				1			10	
Chronic abscess	1			1						1			1	2	2		1	9	
Chondroma			2			1								1	1			5	
Echinococcal cyst		1		1		1	1		1									5	
Hemangioma	1								1	1			1					4	
Coccidioidomycosis granuloma		3																3	
Arteriovenous aneurysm		1			1						1							3	
Localized mesothelioma	3																	3	
Bronchiectatic cyst				1											1		1	3	
Thymoma	1							1							1			3	
Actinomycosis		1																1	
Lipoid pneumonia															1			1	
Hematoma								1										1	
Unclassified			2	4					3									9	
	101	57	34	58	35	39	32	9	21	13	14	11	6	12	12	9	4	467	64.1
Malignant (histologically proved):																			
Primary bronchogenic carcinoma	25	20	33	2	16	11	4	17	1	8	6	8	9	8	5	6	1	180	
Metastatic lesions	17	1	2	1	3	3	3		1	2	2	1	3		1	1		41	
Bronchial adenoma	12			1	1	2	1			1	2	3	4		1		1	29	
Sarcoma	1		1	1	1	1		1	2				1	1	1			11	
Lymphoblastoma			1															1	
	55	21	37	5	21	17	8	18	4	11	10	12	17	9	8	7	2	262	35.9
Total	156	78	71	63	56	56	40	27	25	24	24	23	23	21	20	16	6	729	

[1] MAHON, H. W., AND FORSEE, J. H.: J. Thoracic Surg., 1950, *19*, 724.

[2] THORNTON, T. F., *et al.*: Surg., Gynec., & Obst., 1944, *78*, 364.

[4] HOOD, R. T., *et al.*: J.A.M.A., 1953, *152*, 1185.

[7] GROW, J. B., *et al.*: J. Thoracic Surg., 1948, *17*, 480.

[8] DAVIS, E. W., AND KLEPSER, R. G.: S. Clin. North America, 1950, *30*, 1707.

[9] FINK, D. L.: Minnesota Med., 1951, *34*, 554.

TABLE 2

LIST OF 124 "COIN" LESIONS EXCISED IN PRESENT SERIES

Benign (histologically proved)		
Granuloma (nonspecific)	42	
Tuberculoma	7	
Pneumonitis, chronic	3	
Bronchial cyst	1	
Chondroma	1	
Coccidioidomycosis granuloma	1	
Arteriovenous aneurysm	1	
Lipoid pneumonia	1	
		59
Malignant (histologically proved)		
Primary bronchogenic carcinoma	59	
Bronchial adenoma	5	
Metastatic lesions	1	
		65
Total cases reported		124

mm. per hour was found in only 17 of the cancer patients and in only 7 of the patients with benign lesions.

Six sputum specimens were collected from each patient. Three were studied for tubercle bacilli by microscopy and culture; three were studied for cancer cells. Microscopic examination showed acid-fast bacilli in only one instance. Unfortunately, this was in a third specimen which was returned as a positive test after the patient had undergone a segmental resection for a tuberculoma. With streptomycin protection, his postoperative course was uneventful.

There were 14 patients with sputum cytologic studies which were positive for cancer. In 2 patients with bronchogenic carcinoma, all of the sputum specimens were positive for cancer cells; in 3 patients there were two positive specimens, and in 9 patients there was one positive specimen. There was a single false positive test for each of 3 patients with benign lesions.

This incidence of 14 of 59 (23.75 per cent) cancer patients showing cancer cells in one or more specimen seems low; but the peripheral circumscribed bronchogenic carcinoma does not readily exfoliate into a major bronchus.

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[10] SHARP, D. V., AND KINSELLA, T. J.: Minnesota Med., 1950, *33*, 886.

[11] STOREY, F. S., *et al.*: Surg., Gynec. & Obst., 1953, *97*, 95.

[12] CONDON, W. B.: Thoracic Surgery Seminar, Denver, Fitzsimons Army Hospital, 1952, p. 23.

[13] EFFLER, D. B., *et al.*: Surgery, 1948, *24*, 917.

[14] HUSFELDT, E., AND CARLSEN, C. J.: Thorax, 1950, *5*, 229.

[15] WOLPAW, S. E.: Ann. Int. Med., 1952, *37*, 489.

[16] BELL, I., AND SEALY, W. C.: North Carolina M. J., 1952, *13*, 289.

[17] O'BRIEN, E. J., *et al.*: S. Clin. North America, 1948, *28*, 1313.

[18] ABELES, H., AND EHRLICH, D.: New England J. Med., 1951, *85*, 244.

[19] EFFLER, D. B.: Am. Rev. Tubere., 1951, *63*, 252.

[20] HARE, L., AND BATTERSBY, J. S.: J. Indiana M. A., 1952, *45*, 199.

TABLE 3

NUMBER AND PERCENTAGE OF MALIGNANT "COIN" LESIONS REPORTED IN LITERATURE

	Cases Reported	Malignant	Percentage
1. Hood *et al.*[6]	156	55	35.25
2. Grow *et al.*[7]	78	21	26.92
3. Davis and Klepser[8]	71	37	52.11
4. Mahon and Forsee[4]	63	5	7.93
5. Fink and Asta[9]	56	21	37.50
6. Sharp and Kinsella[10]	56	17	30.35
7. Storey *et al.*[11]	40	8	20.00
8. Condon[12]	27	18	66.66
9. Bell and Sealy[14]	23	12	52.17
10. Husfeldt and Carlsen[15]	24	11	45.83
11. Wolpau[13]	24	10	41.66
12. Effler *et al.*[18]	25	4	16.99
13. Thornton *et al.*[5]	23	17	73.91
14. O'Brien *et al.*[17]	21	9	42.85
15. Abeles and Ehrlich[16]	20	8	40.00
16. Effler[19]	16	7	43.75
17. Hare and Battersby[20]	6	2	33.33

Skin testing for tuberculosis and for various fungi was not done, for it was recognized that a positive test in any case would not exclude the presence of carcinoma and that a thoracotomy would be necessary for a definitive diagnosis.

Angiocardiography was employed to visualize the pulmonic arteriovenous fistula. It was not used in any of the other cases.

Body section roentgenography was not utilized in the present series, but it is recommended as an aid in visualizing calcification. Needle biopsy of a "coin" lesion surrounded by lung should be condemned, for this procedure is associated with a high incidence of complications.

Community and general hospital chest roentgenographic surveys have resulted in the "coin" lesion's becoming a common and important problem. Experience has shown that the tendency to defer surgical excision for observation and prolonged diagnostic tests should be resisted since many of these lesions are malignant.

In summary: One hundred and twenty-four so called "coin" lesions are reported in which a cancer incidence of 52.4 per cent has been found. In the literature, 729 such lesions have been reported and 262 (37.31 per cent) of this group were malignant. A much higher incidence of "coin" lesions are proved to be cancerous in patients more than forty years old. This point is very important and deserves considerable emphasis. Most of the "coin" lesions do not cause symptoms, and a diagnosis of cancer can be made by laboratory procedures in less than one-fourth of the cases. Exploratory thoracotomy is no longer a dangerous procedure. It is recommended as a diagnostic procedure when other measures fail to provide a convincing definition of a particular "coin" lesion.

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May 24, 1955

THE INSPISSATION OF EGG MEDIA FOR THE CULTIVATION OF TUBERCLE BACILLI

The growth of tubercle bacilli from clinical specimens is accomplished most readily on egg-containing media which must be inspissated at 90°C. for coagulation of the heat labile egg materials and for sterilization of the media. The inspissation is done most successfully in inspissators, either those commercially available[1] or those specially built. However, they are expensive and can hold only 100 to 150 tubes at a time. Many laboratories use makeshift devices which are standard laboratory equipment for inspissation. These devices include the hot air oven saturated with water vapor, and the autoclave at 10 pounds of pressure, with sufficient insulation (newspaper wrapping) around the tubes to bring the temperature to the proper height. Adequate media may be prepared by these means with careful watching and attention to detail, but one is never certain of the results with any one group of tubes.

This report is concerned with an improvised inspissator which is adequate for its purpose, is inexpensive, and can be used in any laboratory, not only those primarily engaged in the study of tubercle bacilli.

A household electric roaster[2], with a specially constructed rack holding ninety tubes[3] slanted at the proper angle, can be used as an inspissator. The only modification necessary to adapt the roaster for inspissation is a hole in the lid to accommodate a thermometer set in a sleeve (rubber tubing) for reading of the temperature within the roaster. The roasters are well insulated and will maintain a temperature within 4 to 5 degrees when loaded, despite the inaccuracy of the external temperature control setting. The roaster-rack inspissator is shown in figures 1, 2, and 3.

Sufficient water (3.5 to 4 liters) is placed in the bottom to provide saturated vapor; the rack containing ninety tubes of media is placed directly in the water; and the temperature control is turned to the first setting (150). The temperature of 90°C. is reached within fifteen minutes and the media will coagulate. Continued inspissation for thirty minutes will sterilize the media. Slight manipulation of the temperature setting may be necessary to maintain the 90°C. temperature, but this can be done easily and efficiently. In this laboratory in which 1,000 to 1,200 tubes of media and 600 tubes of drug-containing media for sensitivity testing are prepared each month, the use of four roasters and two inspissators is more than adequate.

A comparison of the cost of the inspissators with that of the roasters follows:

Inspissator 1 (purchased commercially)..... $240.00
Capacity: 144 tubes (150 x 25 mm. screw cap tubes).
Can be run once, or possibly twice, in one day because of the time necessary to reach the proper temperature and humidity.

Inspissator 2 (custom-built, with drawers)..... $750.00
Capacity: 88 tubes.
Can be run twice, or possibly three times, in one day.

[1] Levin-Brandon model.

[2] Westinghouse roasters have been used in this laboratory.

[3] The rack contains eighteen slots, nine on each side. By placing one tube on top of another, five high, in the slot which has been made of proper width so that the tube will not roll, ninety tubes can be accommodated.

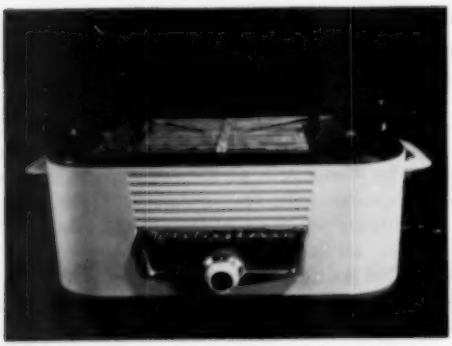

FIG. 1. The assembled roaster-rack combination, showing the slanted tubes

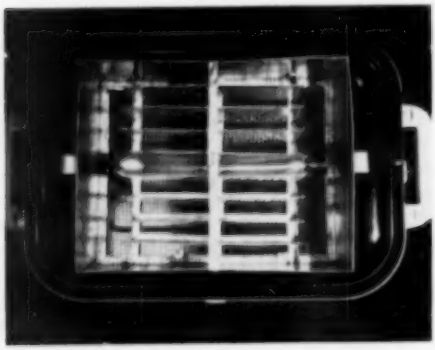

FIG. 2. The rack in the roaster, showing the compartments for adequate slanting

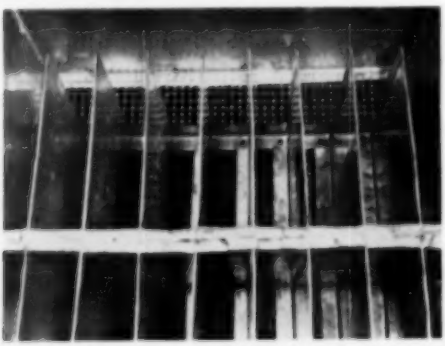

FIG. 3. Details of the rack, showing the manner in which the slant is achieved

Four roasters and racks[4] $200.00
Capacity: 360 tubes (90 tubes per roaster).
Can be run three, or possibly four, times in one day.

The media prepared in the roasters are indistinguishable from those prepared in the commerical inspissators with regard to appearance, ability to grow tubercle bacilli, and stability and dehydration.

In summary: An improvised inexpensive inspissator, made from a household electric roaster, has been described for the preparation of egg media for the cultivation of tubercle bacilli. The improvised inspissator is easy to operate and entirely adequate for its purpose.

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VETERANS ADMINISTRATION HOSPITAL
ALBUQUERQUE, NEW MEXICO

DAVID GALE[5]

June 27, 1955

[4] Cost of one roaster, $30.00; estimated cost of one rack, $20.00 for material and labor. The racks in the present study were made by the hospital maintenance shops.

[5] The writer is indebted to Mr. Thomas Hawkins for fabricating the racks for use in the inspissators.

Books

DIFFERENTIAL DIAGNOSIS. The Interpretation of Clinical Evidence. By A. McGehee Harvey and James Bordley. Pp. 665, W. B. Saunders Company, Philadelphia, Pennsylvania, and London, 1955, Price, $11.00.

The central theme of this book is set forth in its subtitle: "The Interpretation of Clinical Evidence." The method followed in presenting the subject is the highly instructive one of the case conference. Of the several types of case conferences that might have been used to point up the deductive reasoning involved in differential diagnosis, the authors have chosen the clinical-pathological conference. They freely admit that this basis prevents consideration of the diagnosis of diseases not running a fatal course, but point out the inestimable value of the pathologic element of the conference for instructional purposes in establishing definity of diagnosis.

Twelve chapters are devoted to specific clinical entities presenting problems of differential diagnosis, viz., aortic insufficiency, heart failure, pain in the chest, sudden death, failure of urinary excretion, hematemesis and melena, jaundice, hepatomegaly and ascites, lymphadenopathy and splenomegaly, fever of obscure origin, diseases involving the lungs or mediastinum, and meningitis. The clinical field and its diagnostic problems are first discussed, and then a series of illustrative cases are presented.

The cases emanate chiefly from the conferences of three teams at the Johns Hopkins Medical School, William S. Thayer and William G. MacCallum, Louis Hamman and Arnold R. Rich, and, finally, one of the authors, A. McGehee Harvey, and Rich.

The volume has all the interest that attaches to the solution of a difficult problem in the light of a collection of clues. The manner of presentation draws the reader into the analysis of leads and inevitably stimulates his own thinking in each of the illustrative cases reviewed. For this reason the volume has unusual value for both students and practicing physicians.

The format of the volume is convenient and the type setting of text and index is pleasing.

ESMOND R. LONG
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AIRBORNE CONTAGION AND AIR HYGIENE. An Ecological Study of Droplet Infections. By William Firth Wells. Pp. 423, Harvard University Press, Cambridge, Massachusetts, 1955, Price $6.00.

It is easy to understand the desire of an active and creative investigator to relate his particular work to his chosen field within the more capacious limits of a monograph rather than to rely upon the cumulative impact of a series of papers published in a variety of journals at different times. This allows the writer more latitude in the documentation and discussion of his findings and, in addition, provides the reader with much better insight into the personality of the author. With so large a subject to cover, it is fortunate that William Firth Wells has done just this in his latest publication; the resulting volume is one which will be read with attention by all persons interested in the field of air hygiene.

Wells divides his volume into two parts, the first of which he entitles "Airborne Contagium" and it contains a detailed discussion of his conception of the behavior of airborne bacteria-containing particles and of their physics and chemistry. This leads him to a recapitulation of his well-known conception of the role of "droplet nuclei" in the transfer

of infectious agents through the air, in which he summarizes in detail the work he and his associates have done as well as relates it to other studies of inhalation infection.

The second part deals with air hygiene and in it Wells discusses the development of this field and relates it to the basic biophysical characteristics of airborne particles on the one hand and to human ecology on the other. In this section he defines the unit of sanitary ventilation, which he calls the "Lethe," as the basic unit of measurement used to express the efficiency of a given disinfecting agency against standard test organisms, and it is the sanitary equivalent of one air change by ventilation. This definition is a widely accepted one and it has the virtue of relating the rate of aerial disinfection to equivalent air changes. Thus, the two factors become additive and their sum represents the effective total aerial disinfection. He then attempts to quantitate further by defining "Threshold Sanitary Ventilation" as that minimum rate of death or removal of airborne parasites which prevents the epidemic spread of airborne infection in an enclosed space. It is doubtful if this last definition can ever be of more than theoretical importance in view of the many variables which act to transmit infection to any point in time.

It is unfortunate that this book does not possess the clarity of style and exposition to permit the theoretical discussions to be readily understood because there is much in it of great value. However, it does merit careful thought and, while many of his interpretations are controversial and as yet unsupported by valid data, the viewpoints expressed by Wells are of great interest to all people concerned with air hygiene.

The book is beautifully printed for the Commonwealth Fund by The Harvard Press and the inclusive bibliography is especially valuable.

William Lester, Jr.
Hinsdale, Illinois

Tuberculosis Classification Pathogenesis and Management. By Milosh Sekulich. Pp. 316, William Heineman Medical Books Limited, London, 1955.

This small and well-written volume is essentially a second edition of *The Classification of Pulmonary Tuberculosis* (1953). Dr. Sekulich has apparently attempted to correlate all aspects of tuberculosis into a simple four-part classification with multiple subdivisions encompassing all the various manifestations of the disease. His purpose seems ultimately to systematize and thus improve the application of treatment.

The classification is as follows:

I Primary Type
  1. Inflammatory form (Benign Primary)
  2. Caseous form (Malignant Primary)

II Secondary Type
  1. Fibro-caseous form
  2. Fibrous form

The accurate use of this classification appears to require a knowledge of the tuberculin reaction before the onset of illness as well as an ability to interpret accurately the pathologic process from an examination of chest roentgenograms and from other clinical sources. He feels able regularly to distinguish primary from secondary infection by the predominant location of visible lesions in the chest roentgenogram. By contrast with Dr. Sekulich's classification, the National Tuberculosis Association Classification assumes no more knowledge of the patient's disease than is clearly evident to most physicians from the same sources.

His varied and quite specific recommendations for the treatment of different forms of tuberculosis imply differences in the forms of the disease and in their treatment which are difficult to substantiate. Dr. Sekulich does not seem too concerned with the dosage, regimen and other details of chemotherapy. In summary, this reviewer did not find the book applicable to the problems of tuberculosis as he sees them.

ROGER S. MITCHELL
Denver, Colorado

BOOKS RECEIVED

1955–1956 YEAR BOOK OF MEDICINE. Edited by Paul B. Beeson *et al.* Pp. 711, Year Book Publishers, Inc., Chicago, Illinois, 1955, Price, $6.00.

A NEW CLASSIFICATION OF TUBERCULOSIS. By Milosh Sekulich. Pp. 63, William Heinemann Medical Books, Ltd., London, 1955, Price, 3/6d.

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LIBRO DE ACTAS. Tomo II. Pp. 699, XIII Conference of the International Union Against Tuberculosis, Madrid, 1955.

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Statement of Subcommittee on Pulmonary Function

May 20, 1955

The Subcommittee on Pulmonary Function was unanimous in its opinion that the report of the Subcommittee on Pulmonary Function Tests, which appeared in the October, 1950, issue of the AMERICAN REVIEW OF TUBERCULOSIS, was an excellent one and that the advent of new and elaborate physiologic procedures provided no grounds for changing the general philosophy or even, in most respects, the specific recommendations. In order to emphasize this continuity of thought, major portions of the present report will be taken over verbatim from the earlier one, quotation marks being used to identify the source. No attempt will be made to evaluate all available pulmonary function tests since the Subcommittee's orientation remains toward the average hospital in which pulmonary diseases are treated and not toward the larger teaching and research centers.

Clinical Evaluation

"First, it should be emphasized that much helpful information concerning pulmonary function can be obtained by the simple routine clinical examinations, provided that the observer trains himself to seek out such information from the history, physical examination, and fluoroscopy.

"In the history, special attention should be given to diseases or other factors which might alter function of a lobe or of one or both lungs by affecting the thoracic cage, pleura, pulmonary parenchyma, and tracheobronchial tree. Careful inquiry should be made of the patient's reaction to daily activity and to physical stress, both in the past and recently. The importance of such factors as pain, bronchial secretions, and asthma in temporarily reducing lung function must be evaluated. It must also be considered whether the history, especially in relation to dyspnea, is consistent with the clinical observation of, and the results of tests upon, the patient.

"In the physical examination, the contour and mobility of the thoracic cage should be noted. The rate and depth of respiration with special attention to prolonged expiration (suggestive of emphysema or partial airway obstruction) or labored breathing at rest is important. The patient should be observed while stripped to the waist after mild exercise (the effect of the specific intensity of such exercise on normal persons must be known to the examiner); the presence of elevated pulse or respiratory rate and the use of the accessory muscles of respiration should be noted. The patient's degree of daily physical activity at the time must be taken into account. This examination must be repeated at the time the patient is being evaluated for collapse or other surgical therapy, and changes from previous observation should be carefully noted.

"A fluoroscopic examination is considered an integral part of the physical examination not only to obtain information concerning the intrathoracic lesion but also because it can furnish valuable data on lung function. The examiner's eyes must be *well* accommodated. The patient is first examined during quiet breathing. Attention is directed to the movement of the diaphragm, rib cage, to shift of the mediastinum, whether with inspiration or expiration, and to aeration of the lung fields. Inequalities of pulmonary ventilation should be sought in the two lungs and even in the individual lobes. The cardio-circulatory findings are noted. The patient should be observed during slow and rapid deep inspiration and expiration; the speed and uniformity of lung emptying is to be noted. Failure rapidly to empty the lung or lungs

of air may be indicative of partial airway obstruction or of emphysema. If feasible, the fluoroscopic examination may also be repeated in the recumbent position. (Fluoroscopy permits a rough estimate to be made of the relative percentage of ventilation carried on by each lung, but in the occasional case can be in gross error in this regard.)

"Chest X-rays should be taken in deep inspiration and also in expiration to record the fluoroscopic findings, but because of their static nature should not replace direct observation of the actual motions under the fluoroscope. The position of the mediastinum on the inspiratory and expiratory films should be carefully noted. Displacement of the mediastinum toward the opposite side on the expiratory film indicates obstructive emphysema of the lung with the greater degree of radiolucency in expiration. In such cases, the usual X-ray taken only in deep inspiration may fail to give any evidence of obstructive emphysema. The relative position of the leaves of the diaphragm on inspiration and expiration should be compared."

Laboratory Tests[1]

The volume of air moved during breathing can be measured by any of several methods. A graphic record of the breathing pattern can be obtained if a rebreathing spirometer with recording pen is used, and all subdivisions of the total lung volume except the residual volume can be recorded directly. When the recording drum revolves rapidly, the speed with which air moves in and out of the lungs can be deduced from the slope of the tracing. The rate at which the lung is emptied during the vital capacity determinations, as well as the volume of air displaced, can therefore be noted. This method of evaluating expiratory obstruction may be less affected by muscular weakness or incoordination than is the maximal breathing capacity. The maximal breathing capacity can also be determined by using this device and is of great value in quantitating the over-all ability of the patient to move air. From the tracing the depth and frequency of each breath can be determined as well as any tendency to trap air. Comparative studies can be made before and after administration of a bronchodilator. Skill and experience are required in evoking maximal effort from a patient and in handling the apparatus, and spirography is therefore best performed by or under the supervision of a trained person.

There are advantages and disadvantages to spirography and to the other techniques available for studying ventilatory function. The chief disadvantages of the rebreathing spirometer are the resistance to flow and the tendency to "overshooting" which may be present during rapid breathing, even when the valves and soda lime canister are removed. However, because knowledge of the shape of the spirographic tracing is of great importance in the physiologic evaluation and because a fairly comprehensive survey of ventilatory function can be made with this one instrument, the rebreathing spirometer with recording pen is recommended in preference to other types of apparatus. Values for maximal breathing capacity are smaller than those obtained with less resistant systems but are useful for clinical purposes when compared to normal standards obtained with the same type of apparatus.[2]

[1] Two excellent references are now available: (*1*) Methods in Medical Research, vol. 2, Year Book Publishers, Chicago, 1950; (*2*) The Lung: Clinical Physiology and Pulmonary Function Tests, by Comroe, Forster, DuBois, Briscoe, and Carlsen, Year Book Publishers, Chicago, 1955.

[2] Baldwin, Cournand, and Richards have reported normal standards obtained with the Collins Respirometer (Medicine, 1948, *27*, 243). This instrument is widely used and readily

Residual Volume

Knowledge of the residual volume has been a great help in understanding some of the changes associated with emphysema and other conditions involving obstruction of the airways and distention of the lung. However, elevation of this value and of the ratio of residual volume to total capacity usually can be predicted in an approximate fashion from the physical examination, fluoroscopy, inspiratory and expiratory chest films, and spirography. A precise determination requires special equipment and considerable skill and is of practical importance only in the exceptional case.

Exercise Tests

"Since the breathing requirements are not the same in different individuals, the response and tolerance of the patient to exercise is a helpful method of evaluating pulmonary function. For this purpose examinations of the type of the step test or the walking ventilation test are available. It is imperative that the responses be interpreted with respect to the intensity of daily activity to which the subject is accustomed at the time of the test."

Bronchospirometry

Bronchospirometry is an important procedure to determine the relative percentage of function of each lung. The relative ventilation of the two lungs usually can be estimated with reasonable accuracy on the basis of physical examination and fluoroscopy. Bronchospirometry provides a more accurate estimate of comparative ventilation and also indicates the relative oxygen consumption of the two lungs. Individual lung function must always be considered, particularly in patients with low maximal breathing capacity on whom operative procedures are contemplated. However, bronchospirometry is not indicated on the majority of patients whose pulmonary function is under consideration.

Using presently available rubber catheters, particularly those of the Carlens type, topical pharyngeal and endobronchial anesthesia, and a standard twin spirometer with calibrated recording, the technique of the procedure may be relatively simple. The operator should be trained in the technique and have at least one trained assistant. The procedure should be performed fairly frequently by the same team if reliable results are to be obtained and the acquisition and upkeep of expensive equipment are to be justified. Great care must be taken to assure proper placement of the catheter and the absence of leaks.

Minimum Requirements

"The Subcommittee considers the following to be the minimum requirements in evaluating a patient's pulmonary function:

Careful analysis of the history
Physical examination
A fluoroscopic examination which attempts to evaluate the magnitude, speed, and distribution of pulmonary ventilation
Inspiratory and expiratory chest X-rays."
Spirographic evaluation of lung volumes and ventilatory function

---

available. Its air flow characteristics are not ideal and "overshooting" becomes significant at respiratory rates in excess of 100 breaths per minute. It is not sufficiently rugged to stand routine use by the rotating house staff of a busy service. Until such time as a better instrument is available, the Subcommittee, nevertheless, feels that the Collins Respirometer is adequate.

"These minimum requirements can be performed in any hospital or sanatorium dealing with diseases of the chest and will yield sufficient information for the management of the great majority of cases. On the basis of these examinations it may be decided whether any additional, more elaborate investigations are necessary before a proper decision concerning surgical or other therapy can be made."

Of the more difficult procedures, the analysis of arterial blood for oxygen saturation or tension and for carbon dioxide content and tension is possibly the most urgent since, in the presence of advanced disease, these values cannot be gauged with sufficient accuracy on clinical grounds. Knowledge of the oxygen saturation makes possible a more judicious use of oxygen therapy, and the carbon dioxide tension is of particular help in the management of patients with respiratory acidosis.

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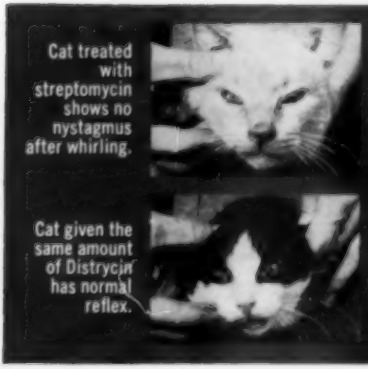
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*Heck, W.E.; Lynch, W.J., and Graves, H.L.: Acta oto-laryng. 41:416, 1953.

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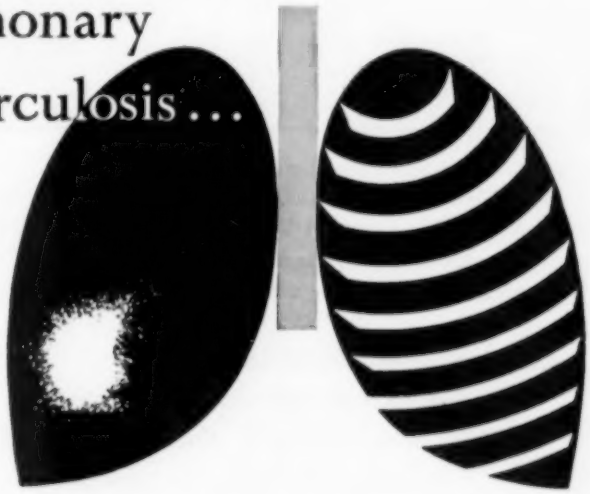

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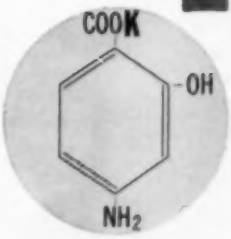

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1. *Molthan, L., Cohen, R. V., and Zarafonetis, C. J. D.: Clinical use of potassium para-aminosalicylate (KPAS). Am. Rev. of Tuberc. and Pulmon. Dis. 71:220 (Feb.) 1955.*

2. *Cohen, R. V., Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations). Read before the American Trudeau Society, Annual Meeting, Milwaukee, Wisconsin, May 23-27, 1955.*

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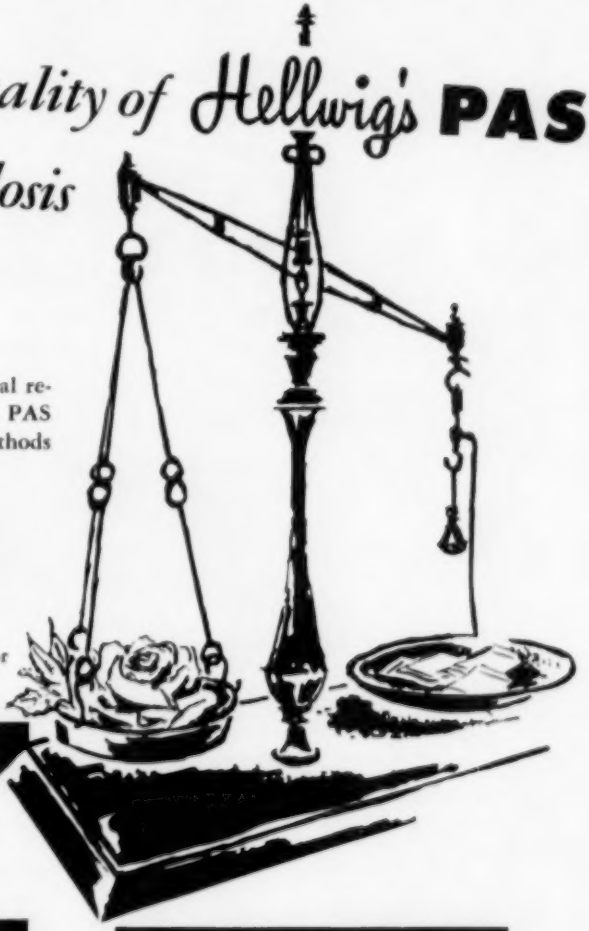

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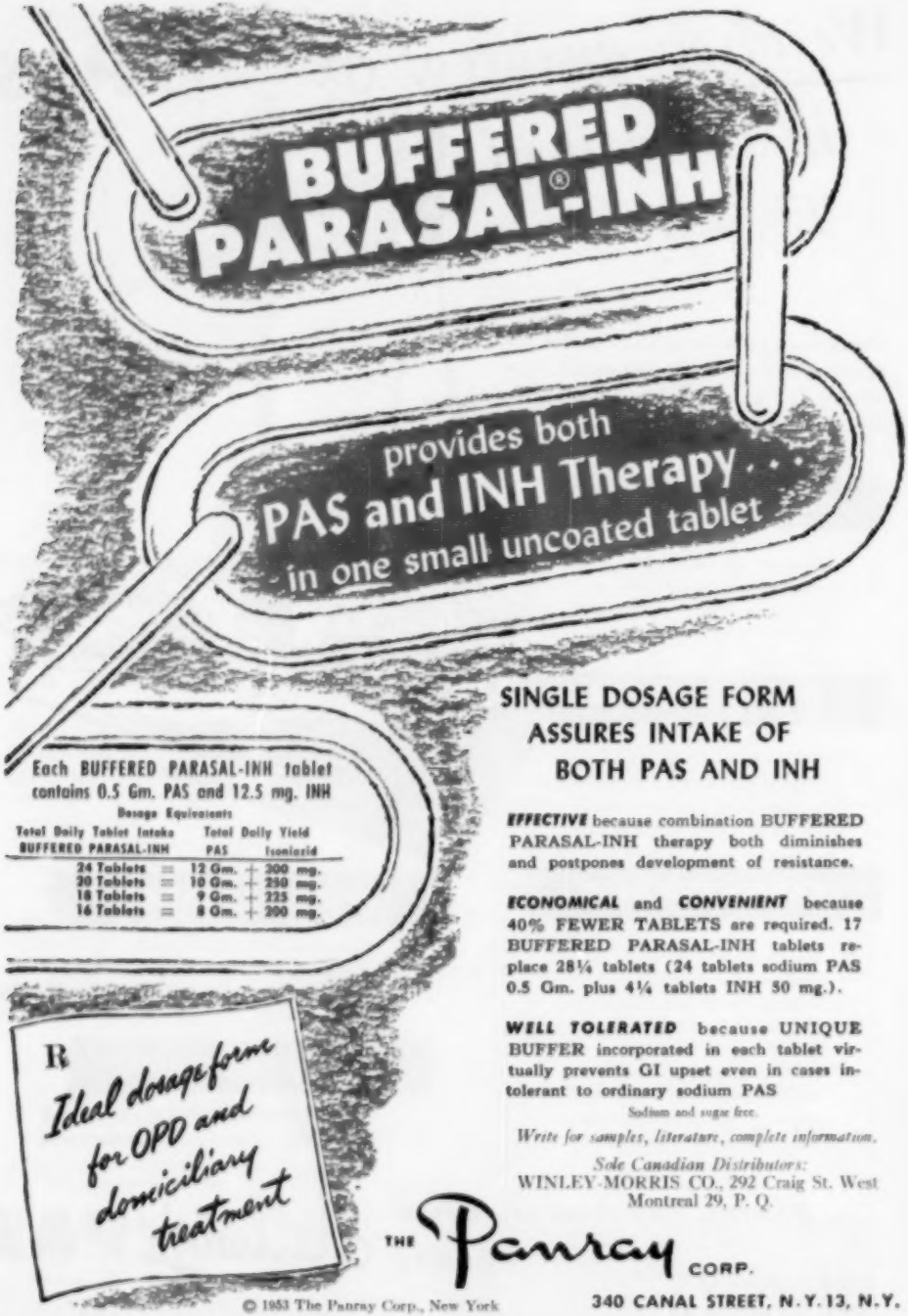

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Sensitivity Testing
of
TUBERCLE BACILLI

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Sensitivities to the commonly employed therapeutic agents are accurately and readily determined using Bacto-Sensitivity Disks containing three concentrations of Dihydrostreptomycin, Streptomycin, Viomycin, PAS (p-Amino Salicylic Acid) and INH (Isonicotinic Acid Hydrazide). Concentrated specimen or pure cultures are evenly streaked on Bacto-Peizer TB Medium and Sensitivity Disks applied. Zones of inhibition of growth following incubation indicate if an organism is sensitive, moderately sensitive or resistant to the various chemotherapeutic agents.

Peizer TB Medium recommended for sensitivity test procedures is easily and readily prepared from Bacto-Peizer TB Medium Base and Bacto-Peizer TB Medium Enrichment (Peizer and Schecter: Am. J. Clin. Path., 20:682:1950). This is a selective medium suitable for primary culture and simultaneous sensitivity determinations of tubercle bacilli from concentrated specimen.

BACTO-SENSITIVITY TEST MEDIA

Bacto-ATS Medium and Bacto-Lowenstein Medium are available in screw capped tubes with added chemotherapeutic agents. The ATS Medium is prepared according to the formula specified by the American Trudeau Society; the Lowenstein Medium according to the Jensen modification. These media are processed under carefully controlled conditions to give rapid optimal growth of the tubercle bacilli.

Bacto-ATS Sensitivity Media and Bacto-Lowenstein Sensitivity Media are supplied in sets of 12 tubes consisting of 2 tubes of control medium without therapeutic agent and one tube each of the following:

Streptomycin 10 mcg./ml.	INH 5 mcg./ml.
Streptomycin 100 mcg./ml.	Streptomycin 10 mcg. and PAS 100 mcg./ml.
Viomycin 10 mcg./ml.	Streptomycin 100 mcg. and PAS 100 mcg./ml.
Viomycin 100 mcg./ml.	Streptomycin 10 mcg. and INH 1 mcg./ml.
INH 1 mcg./ml.	Streptomycin 100 mcg. and INH 5 mcg./ml.

The above media are also supplied in packages of 12 tubes of any one medium. In addition, for more detailed determinations, ATS Sensitivity Media and Lowenstein Sensitivity Media containing Streptomycin 250 mcg., Viomycin 250 mcg., and INH 0.2 mcg. are available in packages of 12 tubes.

These media are supplied in incubator packages which permit preferred horizontal incubation.

Bulletin No. 141 describing Sensitivity Testing of Tubercle Bacilli is available upon request.

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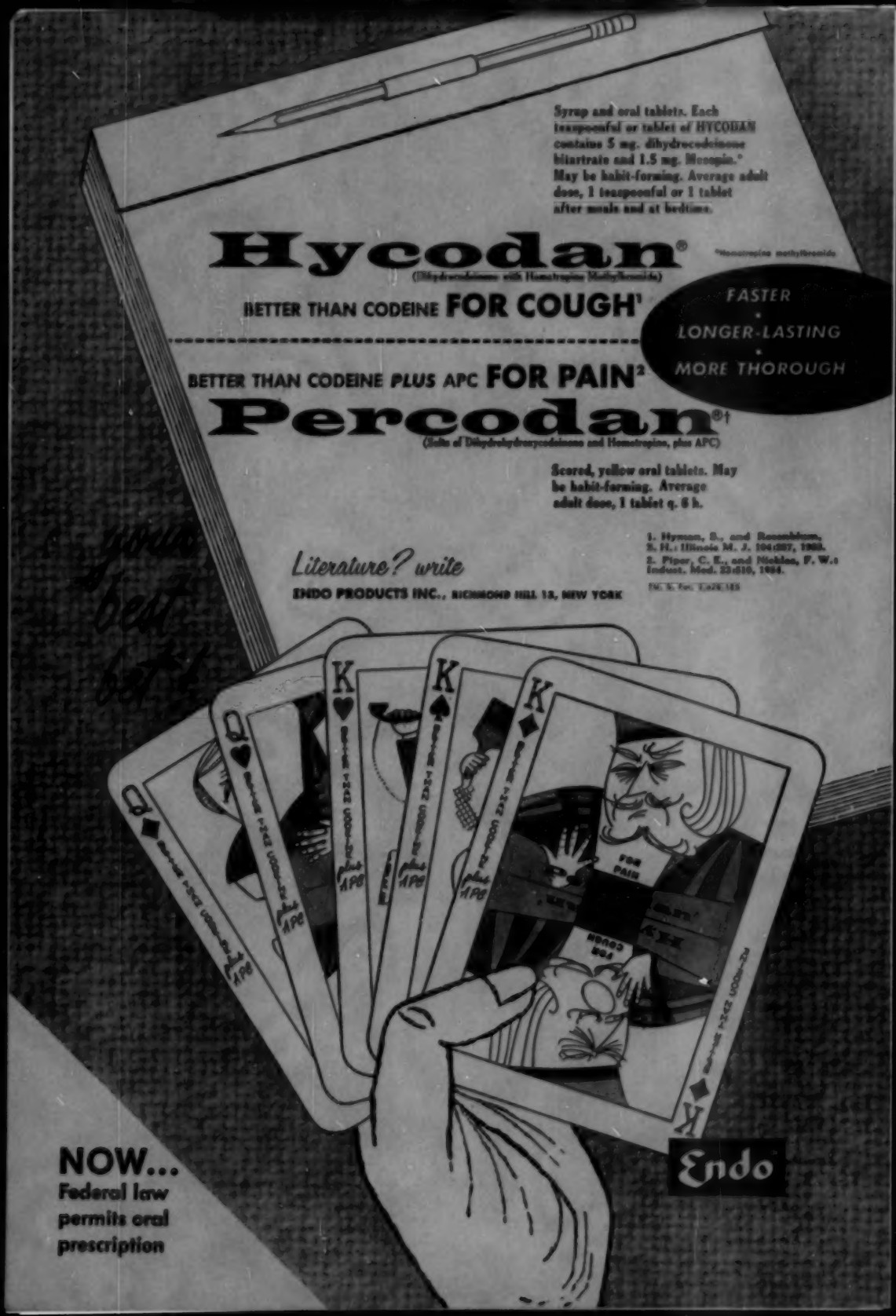
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1. Hyman, S., and Rosenbaum, S. H.: Illinois M. J. 104:287, 1953.
2. Piper, C. E., and Nichlas, F. W.: Indust. Med. 23:310, 1954.
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